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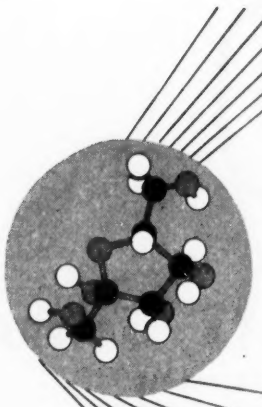

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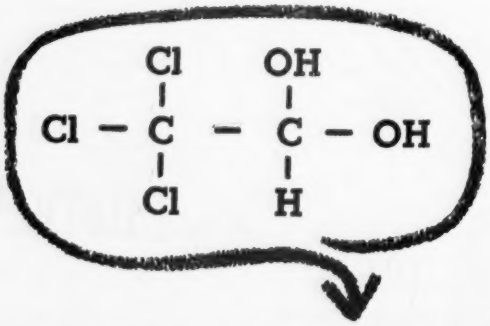

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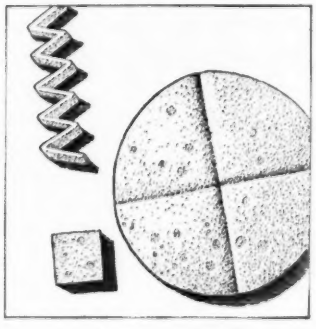

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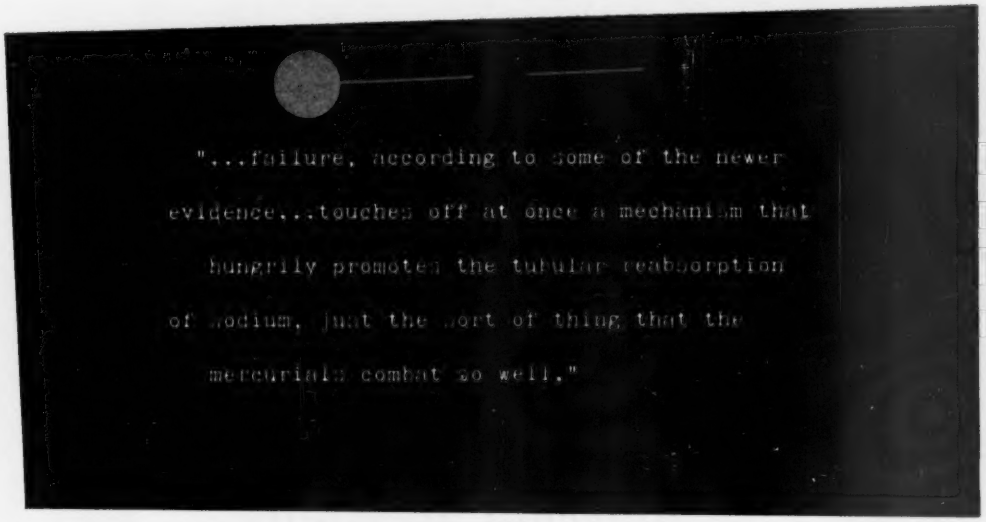
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Volume 248 FEBRUARY 19, 1953 Number 8

DEFECT OF THE INTERATRIAL SEPTUM, WITH THROMBOSIS OF THE PULMONARY ARTERY*

Report of Three Cases

WILMA JEANNE CANADA, M.D.,† FAIRFIELD GOODALE, JR., M.D.,† AND JAMES H. CURRENS, M.D.‡

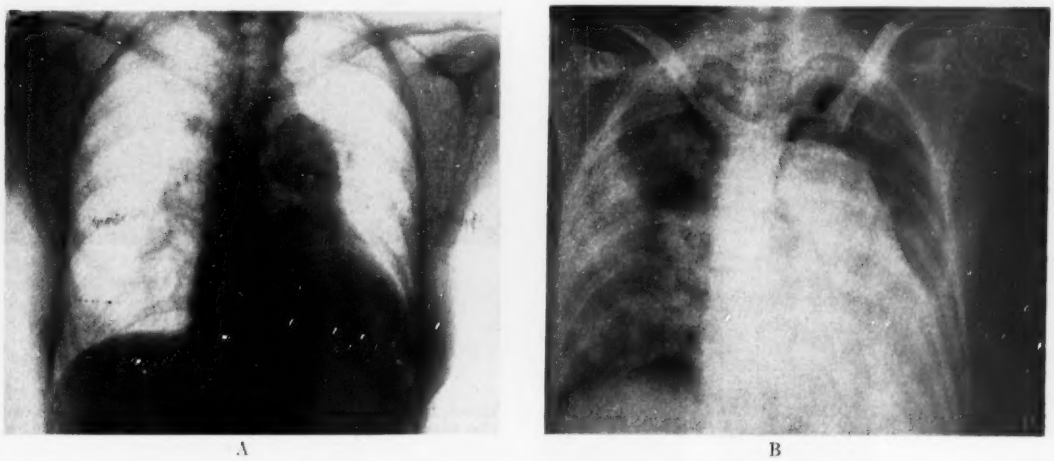
BOSTON

THE combination of a large defect of the interatrial septum and extensive, organized pulmonary-artery thrombosis is rare, although massive thrombosis of the pulmonary artery or its primary branches has been reported with increasing frequency in recent years. It is believed by most pathologists to originate as an embolus from the systemic veins, and occurs postoperatively, in postpartum infections, congenital heart disease, cardiac insufficiency of various causes and a few other rare conditions.[1-8] We were able to find reports of its occurrence in association with a defect of the interatrial septum in only 3,[9-11] and these, in the German, Italian and English medical literature, are similar clinically and anatomically to the cases described below. One additional report was not available to us.[12]

CASE REPORTS

CASE 1.§ G. S. (M.G.H. Autopsy No. 6777), a 34-year-old housewife, was first seen in the Out-Patient Department of the Massachusetts General Hospital in May, 1924, complaining of dyspnea and palpitation on mild exertion. Since the age of 8 years, cyanosis of the fingers and lips had been noted. Physical examination revealed a normal-sized heart and a soft blowing apical systolic murmur. The blood pressure was 115/75.

She was again examined in October, 1929. The cardiac findings were as before, and cyanosis and clubbing of the fingers were noted. An electrocardiogram demonstrated a high degree of right-axis deviation. Roentgenograms of the chest showed a discrete, rounded density measuring about 4 cm. in diameter, lying to the left and below the aortic arch, and displacing the left main bronchus to the right and posteriorly. The right hilus was increased in width and density (Fig. 1*A*).



A B

FIGURE 1. *Roentgenograms of the Chest in Case 1, Showing the Appearance in 1929* (A) *and Four Years Later* (B), *Shortly before Death.*

*From the departments of Pathology and Medicine, Massachusetts General Hospital.

†Resident in pathology, Massachusetts General Hospital.

‡Assistant in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

§This case was previously reported by Burdett and White[12] as primarily of interest from the point of view of defect of the atrial septum. It was also mentioned briefly by Taussig[14] in her monograph.

The patient was again seen in October, 1930, when she complained of cough and hoarseness for the preceding year. There was paralysis of the left vocal cord. Marked accentuation of the pulmonic second sound was noted.

In January, 1931, she was admitted to the hospital for the first time because of increasing cough and anorexia. Physical examination revealed cyanosis of the lips and fingers, clubbing of the fingers and orthopnea. The heart was enlarged, the border of cardiac dullness extending 1 cm. to the left of the midclavicular line. There was a loud apical systolic murmur, which was transmitted to the left axilla. The pulmonic second sound was unusually loud. The blood pressure was 110/65. The hemoglobin was 15 gm. per 100 cc., and red-cell counts varied from 6,010,000 to 6,800,000. The vital capacity was 1220 cc. on 1 determination.

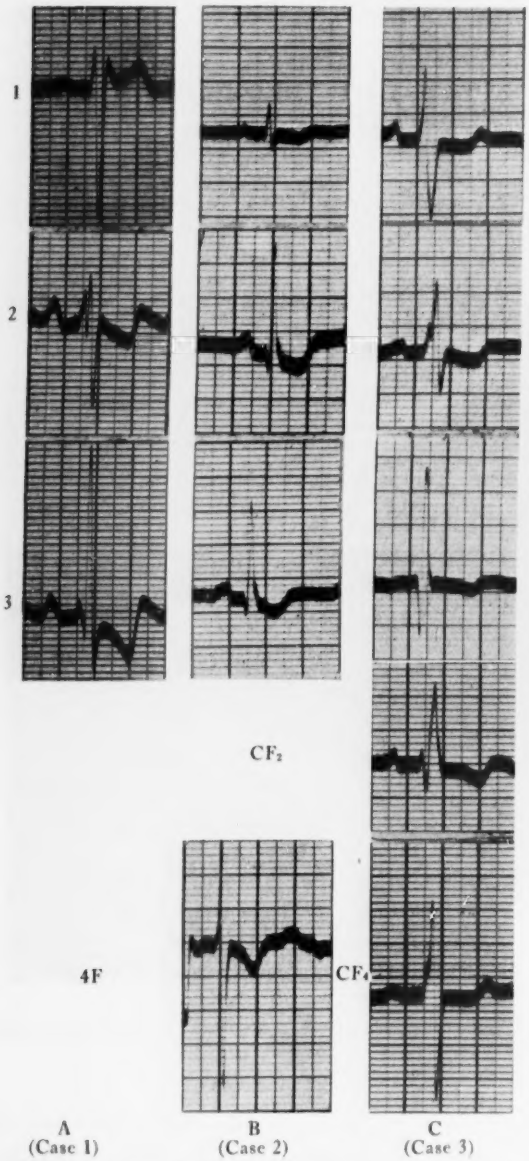


FIGURE 2. *Electrocardiograms in Cases 1*(A), *2*(B) *and 3* (C). *Tracings* A *and* C *demonstrate impairment of intraventricular conduction complex (QRS complex=0.12 second) of the right-bundle-branch type. Tracing* B *was considered to represent a "balancing effect" due to hypertrophy of the left and right ventricles since the patient had significant arterial hypertension.*

In February, 1932, the patient entered the hospital for the second time. For the 4 months before re-entry she had experienced recurrent attacks of dull, severe pain in the middle portion of the chest and back associated with dyspnea and weakness. On physical examination she was cyanotic, and respirations were of the Cheyne-Stokes type. There was a loud systolic murmur at the apex, and a short, harsh apical diastolic murmur was heard for the first time.

After being an invalid for a year, the patient was readmitted to the hospital in January, 1933, suffering from severe dyspnea and severe pain in the upper back and neck. For 5 days before entry she had coughed up bright-red blood in small amounts. Physical examination was unchanged. During the hospital stay she complained of pain in the left side of the chest that was aggravated by breathing, and she raised bloody sputum. A roentgenogram demonstrated coarse, mottled areas of increased density throughout both lung fields, more marked on the right. The mass in the left hilus previously described was larger (Fig. 1*B*). An electrocardiogram (Fig. 2*A*) indicated impairment of intraventricular conduction of the right-bundle-branch variety. She died quietly, at the age of 43, 2 weeks after entry.

FIGURE 3. *Appearance of Heart and Lungs after Fixation in Case 1.*

Arrows point to organized thrombi lying in both main pulmonary arteries. The hypertrophy of the right ventricle is apparent.

At autopsy the main pulmonary artery measured 5.5 cm. in diameter and contained a large yellowish-grayish-red thrombus beginning 2 cm. above the pulmonary valve and extending into both branches of the pulmonary artery (Fig. 3). On the left, the thrombus extended into a large branch of the artery, 1 cm. in diameter and supplying the area of an infarct measuring 8 by 11 cm. in the lower lobe of the left lung. On microscopical examination this infarct appeared fairly recent. On the right the thrombus extended for a distance of 11 cm. beyond the bifurcation of the main pulmonary artery. Both main branches were occluded, with the exception of an opening along the posteroinferior portion of each vessel that barely admitted the index finger. The walls of these passageways were therefore formed by the intima of the pulmonary artery below and posteriorly and the thrombus above and anteriorly.

The exposed part of the thrombus was smooth, whitish and glistening, and the base was firmly adherent to the vessel wall. The thrombus varied in appearance throughout its substance, but was for the most part firm, homogeneous and whitish yellow, with numerous scattered cystic areas of degeneration, measuring up to 0.5 cm. in diameter. It was laminated, with alternating sheets of yellowish-white and grayish-white material. On microscopical examination the thrombus appeared well organized and laminated and firmly adherent to the vessel wall. The proximal portion of the pulmonary-artery wall contained several atheromatous plaques measuring up to 8 mm., and the smaller branches extending well into the lung parenchyma also demonstrated numerous yellowish plaques, some of which had ulcerated. These distal branches were also greatly dilated, several within the lung substance being 1 cm. in diameter. On microscopical examination the medium and large-sized branches of the pulmonary artery revealed extensive fibrous intimal thickening with some atheroma formation. A few small vessels contained recent organizing and old recanalized thrombi.

The lungs otherwise contained excessive fluid and fibrosis at both apexes, suggesting old tuberculosis. There was microscopical evidence of early bronchopneumonia.

The heart extended 14 cm. to the left and 4.5 cm. to the right of the midsternal line. The right atrium was dilated and estimated to be a third larger than normal. The anatomic apex was formed by the right ventricle. The wall of the right atrium measured 2 to 4 mm. in thickness. There was an oval defect, 3.5 cm. in diameter, in the interatrial septum just above the tricuspid valve. The superior border of the defect was formed by a semilunar, thin, fibrous band and muscular tissue suggesting the annulus ovalis; the edges were smooth, with no evidence of vegetations or ulceration. There was no Eustachian valve. The musculi pectinati were greatly hypertrophied. The myocardium of the right ventricle was strikingly hypertrophied, measuring 11 mm., and the cavity was dilated. The left atrium was not enlarged. The wall of the left ventricle was 14 mm. thick. There was slight thickening along the free edges of the mitral valve, but otherwise the valves were normal, the mitral being 9 cm., the aortic 5.5 cm., the tricuspid 13 cm., and the pulmonary 9.5 cm.

There was slight atherosclerosis of the first portion of the left coronary artery, and moderate atherosclerosis of the ascending aorta. On microscopical examination no evidence of syphilis was found. The liver weighed 1450 gm., with slight evidence of chronic passive congestion. The kidneys weighed 250 gm.; moderate cortical scarring was observed. There was an unusual preponderance of the cells of the erythroblastic series in the bone marrow. The leg veins were not examined.

Case 2. L. M. (M.G.H. Autopsy No. 14,773), a 70-year-old businessman, was first admitted to the hospital in May, 1943, for a prostatic operation. At the age of 30 he was first found to have a heart murmur and was issued substandard life insurance. However, 25 years later, he was granted standard life insurance. He had experienced slight dyspnea on exertion for several years before admission, but no orthopnea. There was no past history of rheumatic fever.

On physical examination, the heart was slightly enlarged, with the left border of dullness 1 cm. to the left of the midclavicular line. No murmurs were heard. The pulmonic second sound was slightly accentuated and was greater than the aortic. The blood pressure was 145/75. The pulse was regular at a rate of 100. An electrocardiogram demonstrated nonspecific RS-T and T-wave changes. The patient was taking digitalis leaf, 0.1 gm. daily. A suprapubic prostatectomy was done without sequelae.

He was next seen by his physician in February, 1947, when he complained of swelling of the ankles during the preceding 4 years. He had discontinued the use of digitalis because of nausea. One year previously, he had noted increasing exertional dyspnea.

Physical examination revealed a moderate malar flush. A cervical-vein pulsation was visible just above the clavicle. A few coarse, moist rales were heard at the right lung base, posteriorly. The heart rhythm was irregular at a rate of 95, and Grade 2 apical and pulmonic systolic murmurs were heard. The pulmonic second sound was still accentuated and greater than the aortic. The liver edge was palpable 5 cm. below the right costal margin, and there was moderate pitting edema of the legs. A roentgenogram of the chest (Fig. 4) showed the heart to be enlarged, measuring 15.8 cm. in transverse diameter, with an internal thoracic diameter of 23 cm. By fluoroscopy, the hilar shadows were unusually prominent and pulsatile. The peripheral lung fields were clear. An electrocardiogram demonstrated a normal sinus rhythm, with frequent premature auricular systoles. The blood pressure had increased to 210/140.

The urine gave a +++ test for albumin. The hemoglobin was 16 gm. per 100 cc. The blood nonprotein nitrogen was 30 mg. per 100 cc.

The patient was placed on a low-sodium diet and treated with digitalis, ammonium chloride and mercurial diuretics. On this program he improved. The blood pressure continued in the range of 220/130.

During the subsequent 3 years he got along quite well, but continued to have moderate dyspnea on exertion, with orthopnea requiring 2 or 3 pillows for relief. The blood pressure decreased to the range of 180/105. The orthopnea increased, and in September, 1949, he was using 4 pillows at night. The auscultatory findings remained about the same except for an increase in the intensity of the first heart sound at the apex, and of the apical systolic murmur. Auricular fibrillation appeared in 1948, but the ventricular rate was well controlled with digitalis. An electrocardiogram (Fig. 2*B*) was considered to demonstrate a balancing effect between right-ventricle and left-ventricle hypertrophy. The pattern did not change appreciably during the last 4 years of life.

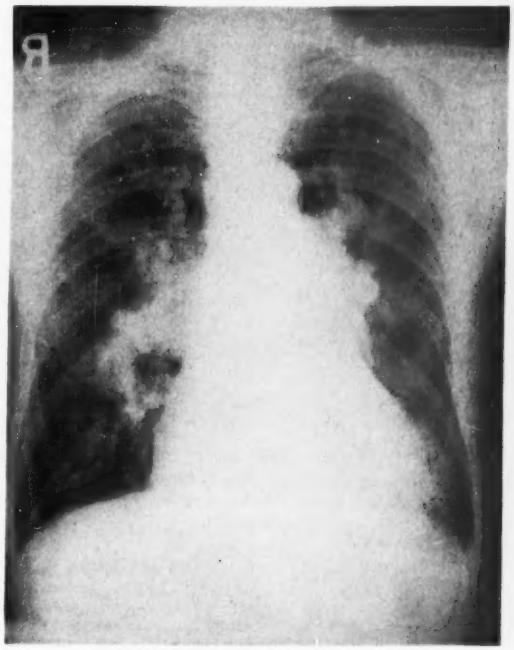


Figure 4. *Roentgenogram of the Chest in Case 2. The prominent features include extreme enlargement of the hilar shadows, with a typical "comma sign" on the right, and relative avascularity of the peripheral lung fields.*

In December, 1949, it was necessary for the patient to sleep in a chair. He became weaker but still continued to spend a few hours at his office each day. During the last year of life the hilar pulsations, which had been accentuated previously, appeared to be diminished to absent on fluoroscopic examination.

In April, 1951, he complained of increasing dyspnea and an acute pain in the left anterior portion of the chest. When he was examined 2 weeks later, an unusually loud pulmonic

second sound was heard along the left sternal border. Signs of fluid were present over the left lower part of the chest. He was referred to the hospital, where 1350 cc. of serosanguineous fluid was removed from the left pleural cavity. He died quietly that night, at the age of 78 years.

At autopsy the main pulmonary artery and its primary branches were tremendously dilated, the right measuring 8 cm. and the left 5.5 cm. in circumference. Both primary branches were filled with an old laminated reddish-gray thrombus, which was firmly adherent to the posterior wall of the vessel. The main pulmonary artery was free of thrombus, which began 1 cm. distal to the bifurcation bilaterally. At the bifurcation, on the left side the entire circumference of the artery was covered by thrombus, but on the right a 2 cm.-area of the circumference of the vessel anteriorly was not involved. A few centimeters distal to the bifurcation of the main pulmonary artery, no lumen was visible on cross sections of the vessels. On the right the thrombus extended 8 cm. distally from its origin, or just beyond the first major branches, although a few of the small peripheral vessels contained thrombi, many of which were dilated to as much as 1 cm. in diameter. On the left it extended as far into the peripheral vessels as they could be dissected. The intima of the main pulmonary arteries showed only minimal atherosclerosis, but the walls of the small peripheral arteries were thickened to as much as 2 mm.

FIGURE 5. *Appearance of the Heart at Autopsy in Case 2. The defect of the atrial septum filled with cotton is seen from the left atrium. Inferiorly, the thickness of the right-ventricle wall is apparent.*

Microscopical examination showed the main pulmonary artery to be markedly atherosclerotic. All sections revealed massive laminated thrombus in varying stages of organization adherent to the vessel wall at the site of atheromatous plaques. There was diffuse, moderately severe, acute and chronic inflammatory reaction within the media and adventitia of the vessel. The blood vessels in the adventitia appeared dilated and congested.

The lungs weighed 1250 gm. The right lung was firm and moderately congested. The left lower lobe contained multiple infarcts of varying ages. Both bronchial arteries were atherosclerotic, and the right was slightly larger than normal, measuring 5 mm. in diameter. On microscopical examination virtually all vessels showed moderate to severe changes: a few small arteries and arterioles demonstrated obliteration of their lumens by concentric layers of fibrosis, whereas others contained old, organized thrombi with recanalization. In the areas of infarction, many arteries were filled with old and recent thrombi.

There was a small serous pleural effusion on the right, and 500 cc. of serosanguineous fluid was found in the left pleural cavity.

The heart weighed 500 gm. The wall of the right ventricle was considerably hypertrophied, being 8 mm. in thickness, and focal fibrosis was present on microscopical examination. The left ventricle was slightly thickened, measuring 18 mm. The left atrium appeared normal in size. The right atrium was dilated to roughly twice normal capacity, but the wall was of normal thickness. The endocardial surfaces appeared normal and were free of thrombi. There was a large oval defect in the interatrial septum, 4.5 cm. in greatest diameter and surrounded by smooth endocardium (Fig. 5). The septal defect in this case was identical to that in Case 1, in which, however, the inferior edge of the defect extended to the tricuspid valve, whereas in Case 2 it extended only to a point 2 cm. above the valve. The valves were normal. Mild coronary atherosclerosis and calcification were present.

The liver weighed 970 gm., and slight cardiac cirrhosis was present. The spleen was normal, and there was slight nephrosclerosis. No thrombi were present in the femoral, popliteal or calf veins. An incidental finding was an old, large, encapsulated subdural hematoma, overlying the left cerebral hemisphere.

CASE 3.* A. N. (M.G.H. Autopsy No. 15,163), a 52-year-old woman, entered the hospital for the first time in May, 1947, because of dyspnea and swelling of the legs. One and a half years before admission she had had an episode of severe substernal pain, after which peripheral edema had developed. Cyanosis of the nail beds, gradually increasing dyspnea and some orthopnea also appeared during that time, and despite digitalis, diuretics and limited activity, the symptoms persisted. As a child she had always been weaker than her playmates, and she had had frequent fainting spells. She had always been somewhat short of breath, and a heart murmur had been present as long as she could remember. She had, however, led an active life and had completed 3 pregnancies without difficulty.

Physical examination revealed a thin, dyspneic and orthopneic woman, with slight clubbing and appreciable cyanosis of the fingers. The neck veins were distended. The heart was enlarged, but the rhythm was regular. The second sound in the pulmonic and mitral areas was moderately accentuated. A rumbling apical diastolic murmur was repeatedly described. A few moist rales were heard at each lung base, and the liver edge was palpable at the level of the iliac crest in the midclavicular line. The legs were edematous to the knees. The blood pressure was 210/110.

The urine had a specific gravity of 1.018 and gave a ++ reaction for albumin. The red-cell count was 4,000,000, and the white-cell count 7500, with 77 per cent neutrophils. The nonprotein nitrogen was 64 mg. per 100 cc. The blood Hinton reaction was negative. An electrocardiogram (Fig. 2*C*) revealed normal rhythm at a rate of 70, with impairment of intraventricular conduction of the right-bundle-branch variety. A roentgenogram of the chest demonstrated considerable enlargement of the heart and unusual enlargement of the main pulmonary artery and its branches. The vascular markings in both lung fields were accentuated.

On treatment with digitalis, a low-sodium diet and diuretics the patient lost 8 pounds in weight and her condition was much improved. The nonprotein nitrogen decreased to 36 mg. per 100 cc. during the hospital course.

On a similar therapeutic program in addition to limited activity she did well for the next 3 years, when pain in the left lateral wall of the chest and a sensation of precordial tightness developed. After this the dyspnea, which had been minimal, became more pronounced, and the lips more cyanotic, and she was admitted to the hospital for the second time.

The lips and fingers were cyanotic. Examination of the heart again revealed a moderate apical diastolic rumbling murmur and unusual accentuation of the second heart sound in the pulmonic area. There were a few moist rales at the lung bases, and the liver edge was just palpable on inspiration. There was no ankle edema. The blood pressure was 160/100. Urinalysis revealed a ++++ reaction for albumin, and the sediment contained 50 red cells and 10 white cells per high-power field. The hemoglobin was 17.8 gm. per 100 cc., and the white-cell count was 10,500, with 75 per cent neutrophils. The nonprotein nitrogen was 29 mg. per 100 cc. An x-ray film of the chest was unchanged from that of the previous admission. On a low-sodium diet, mercurial diuretics and digitalis the patient again improved.

The third and last admission was in November, 1951, at the age of 57. She had carried on fairly well on limited

*This case was previously reported in the Case Records of the Massachusetts General Hospital.[13]

activity and had required no mercurial injections for 1 year. Three weeks before entry sharp pain in the left lateral part of the chest, aggravated at times by respiration and necessitating lying on the left side for relief, developed. There were no chills, cough, hemoptysis or change in the dyspnea or orthopnea. However, the cyanosis was more pronounced.

Physical examination revealed a cyanotic woman in moderate respiratory distress. There was an area of dullness in the left axilla, with crackling inspiratory rales. The heart examination was unchanged. Although the liver edge was not palpable there was tenderness in the right upper quadrant. There was no peripheral edema.

The temperature was 100.5°F., the pulse 100, and the respirations 40. The blood pressure was 150/80.

The hemoglobin was 19.3 gm. per 100 cc., and the white-cell count 10,900, with 87 per cent neutrophils. A chest roentgenogram showed that the heart had increased somewhat in size since the previous examination, and there appeared to be some enlargement of the right interlobar artery. There

FIGURE 6. *X-ray Film of the Chest in Case 3 during the Last Hospital Admission and One Day Before Death. The heart is large, and the prominent pulmonary artery on the right is easily visible.*

was a zone of mottled increased density lying laterally in the left mid-lung field, probably in the upper lobe (Fig. 6).

The cyanosis and dyspnea increased and the patient died quietly on the 2d hospital day.

At autopsy the main pulmonary artery was 9.0 cm. in circumference, and both branches were moderately dilated, the right measuring 3.2 cm. and the left 3.5 cm. in diameter. Starting at the bifurcation, which was 2.5 cm. above the pulmonary valve, both main arteries were almost occluded by thrombi, which extended into the periphery of both lungs to the terminal branches (Fig. 7). Around the periphery each thrombus was grayish yellow, firm and flecked with small bits of firm, white calcium deposits, and was closely adherent to the wall of the artery except for a small area on the inferior portion of each vessel, which barely admitted an instrument the size of a lead pencil. Around this small lumen each thrombus was reddish brown and friable and appeared recent. The thrombus was laminated, the recent reddish areas gradually becoming more firm, grayish yellow and older toward the periphery. In the medium and small arteries the thrombi were all of recent origin. Microscopical examination of the adventitia of the main pulmonary arteries showed many small dilated and congested blood vessels. The intima of the terminal branches of the pulmonary artery was markedly atherosclerotic, with thickening of the walls, but no thromboses were present. The right bronchial artery was found without difficulty and measured 1.0 mm. in diameter. On microscopical examination its intima was considerably thick-

FIGURE 7. *Cut Surface of the Right Lung in Case 3, Showing Extensive Thrombosis of the Right Pulmonary Artery at the Level of the Primary Branches.*

ened, and there was a moderate amount of calcium in the media. The left bronchial artery could not be demonstrated.

Each pleural cavity contained 1000 cc. of free clear, straw-colored fluid, and there was a small focal area of dense fibrous adhesions at the right base lateroposteriorly. The lungs weighed 1350 gm., and there were 2 recent infarcts, 1 in the

FIGURE 8. *Defect of the Atrial Septum in Case 3, Observed from the Right Atrium.*

right middle lobe laterally, 9.5 cm. in diameter, and the other in the left upper lobe anteriorly, 11 cm. in diameter.

The heart weighed 400 gm. The right atrium had a thickened endocardium and was markedly dilated. One centimeter above the tricuspid valve was a large defect of the interatrial septum, measuring 4.0 by 3.0 cm. (Fig. 8). There were fenestrations involving the septum that constituted the inferior border. On the endocardial surface of the right ventricle was a large, firmly adherent, partially calcified thrombus. The right ventricle was hypertrophied, its wall being 0.9 cm. thick, and tremendously dilated, having a capacity approximately three times that of the left ventricle. The left-ventricle wall measured 1.1 cm. in thickness. The cavity was normal in size, but the entire left ventricle appeared to be pushed laterally by the enlarged and dilated right ven-

tricle. The myocardium throughout showed small areas of focal fibrosis. The valves were normal, the mitral measuring 7.9, the tricuspid 12.5, the aortic 6.5, and the pulmonary 9.5 cm.

The coronary arteries and aorta were moderately atherosclerotic. The femoral, popliteal and calf veins revealed no thrombi. The liver and kidneys were normal.

Discussion

For the past twenty years it has been possible clinically to diagnose defects of the interatrial septum with a high degree of accuracy.[16-19] The characteristic finding on auscultation is moderate accentuation or splitting of the pulmonic second sound, with or without a pulmonary systolic murmur. There is usually electrocardiographic evidence of pronounced hypertrophy of the right ventricle or right-bundle-branch block. The roentgenographic findings are characterized by a small aortic shadow and variable prominence of the shadows of the pulmonary artery and lung hilus, which on fluoroscopic examination are usually observed to pulsate. By means of cardiac catheterization[20] an increase in the oxygen saturation of the blood from the right atrium over that in the venae cavae is strong corroborative evidence for the diagnosis of a defect of the interatrial septum. Passage of the catheter into the left atrium from the right atrium confirms the diagnosis.

Clinically, the diagnosis of organizing pulmonary-artery thrombosis may be suspected when a patient has one or more pulmonary emboli and fails to regain normal health. The relatively nonspecific symptoms of dyspnea, orthopnea, cyanosis, chest pain and cough, when combined with few pulmonary physical signs, are also suggestive. Electrocardiographic changes immediately after a massive embolus are those of acute strain of the right side of the heart, but those of a long-standing thrombosis are similar to those seen in chronic cor pulmonale from any cause.

The characteristic x-ray picture of embolism of the pulmonary artery has been recognized for many years[21] and has recently received attention in this country.[22] The usual feature of massive embolism or thrombosis involving one or both primary branches of the pulmonary artery is the prominent pulmonary arterial shadow, which is limited to the hilar region or inner third of the lung field. The vascular shadows of the peripheral lung fields are less prominent than normal. There may be an abrupt line of demarcation at the end of the prominent arterial shadow. Cardiac catheterization is of little diagnostic help except merely to suggest obstruction in the pulmonary artery, when the catheter fails to enter the pulmonary artery and its right and left branches. Angiocardiography would be helpful in localizing obstruction.

The hemodynamics of a defect of the interatrial septum have been clarified in part by catheterization of the right side of the heart and the pulmonary artery.[20] The fact that cyanosis is not present in the majority of cases or, if present at all, usually occurs in the later years of life indicates a predominant shunting of blood from the left to the right atrium.[23] This, in turn, means that a positive pressure gradient exists from the left to the right atrium, and the amount of blood shunted would be dependent upon the size of the defect and the degree of the pressure gradient. However, a shunt may also exist from the right to the left atrium and may be sufficiently great to result in cyanosis under certain circumstances, such as exercise, congestive heart failure and chronic pulmonary disease. A possible mechanism in the production of cyanosis that has been suggested is a direct flow of blood from one of the venae cavae into the left atrium by virtue of its anatomic relation to the interatrial defect. It is therefore apparent that although a shunt probably exists in both directions at the same time, that from left to right is much greater and accounts for the right-ventricle hypertrophy, the eventual right-ventricle dilatation and the lack of cyanosis.

The explanation why patients with defects of the interatrial septum eventually have congestive heart failure after getting along so well for many years remains a mystery. There is not necessarily any correlation between size of defect and length of survival. The onset of auricular fibrillation is at times a precipitating factor of cardiac insufficiency and congestive circulatory failure. Case 2 is a near record for length of survival and indicates that such a congenital defect may not necessarily preclude a long and active life.

Cardiac catheterizations have demonstrated that right-ventricle and pulmonary-artery pressures are normal at rest in half or more of these patients.[24] This suggests that the arterial bed has become adapted to the increase in right-ventricle output incident to the preponderant left-to-right atrial shunt. The accentuation of the second heart sound in the pulmonary area in these cases suggests pulmonary hypertension, but this accentuation may also result from dilatation of the valve ring, such as that associated with syphilitic aortitis. An apical rumbling diastolic murmur is often present, but does not necessarily indicate the presence of an associated mitral stenosis (Lutembacher's syndrome),[25] and may be produced by relative tricuspid stenosis, resulting from dilatation of the right ventricle. None of the patients in the cases reported or reviewed above had mitral stenosis.

The cause of pulmonary hypertension when it does exist in patients with a defect of the interatrial septum may be sclerosis of the pulmonary arterioles, pulmonary embolism or, as in the 3 cases reported above, pulmonary-artery thrombosis.[27-29] Cardiac catheterization in 1 such patient revealed pulmonary hypertension, and autopsy eight months later showed sclerosis of pulmonary arterioles and thrombosis of some small arteries.[30] Post-mortem

studies have disclosed definitely more atherosclerosis than normal in patients with defects of the atrial septum, and since the pressures are not elevated in all cases, this may be attributable to the previously demonstrated increased volume flow through the pulmonary circuit.[21] It is probable, however, that these patients had intermittent pulmonary hypertension.

Of the 3 patients discussed above, only 1 (Case 2) manifested appreciable atherosclerosis of the pulmonary arteries (Grade 3 on the basis of Grade 1 to 4) or pulmonary arterioles (Grade 3). In spite of this anatomic evidence of long-standing pulmonary hypertension, he had only a minimal degree of cyanosis.

Microscopical examination of the thrombi in each case indicated that they were at least months, and probably years, old. Clinically, it was difficult to determine when they occurred, although in Case 3 the episode of severe chest pain four years before death, followed by the edema, dyspnea, orthopnea and cyanosis, as well as the radiologic appearance of an enlarged pulmonary artery, suggested the occurrence of an embolism at that time. In this case, the mural thrombus in the right ventricle may have been the source of the embolus.

Two questions are raised by the associated conditions present in these 3 cases: Does a defect of the interatrial septum predispose to the formation of pulmonary thrombosis? And does the presence of the defect have any effect in prolonging life in the face of a massive pulmonary-artery thrombosis? Any answers to these questions must remain in the realm of speculation, although certain facts may shed light upon the problems.

Many of the conditions known to predispose to the formation of thrombosis in the pulmonary vessels have been mentioned previously. Factors in common are internal changes in the vessel, such as atherosclerosis and embolism, and increased pulmonary blood volume, with a decreased rate of blood flow. Congenital heart lesions in general may provide both these factors, particularly in the presence of congestive heart failure, although it is known that apparently spontaneous thrombosis may occur in congenital heart disease even without failure. Thus, there seems to be evidence that a defect of the atrial septum probably predisposes to the formation of pulmonary-artery thrombosis. However, the fact that in the literature only a few cases can be found in which the two conditions were associated, in the absence of other complicating lesions, fails to provide statistical support for this assumption.

In the 3 cases in the literature similar to the 3 reported above, all the patients were in the sixth decade of life, and the 3 described above were forty-three, fifty-six and seventy-eight years of age at the time of death. In several large series of patients with defects of the atrial septum the average age at death was between thirty and fifty years.[16, 17, 19, 20] Most of the reported patients with massive pulmonary-artery thrombosis alone have died between the ages of forty and sixty, though a few cases have been seen in children. Despite the tenuous evidence afforded by these series of cases, it is conceivable that the presence of a defect of the interatrial septum will prolong life to some extent when the pulmonary arteries are markedly occluded by thrombi, if adequate collateral circulation exists. It is possible that some of the back pressure from the obstructed pulmonary circuit can be directed through the septal defect and into the systemic circulation via collateral vessels such as the bronchial arteries.[22] In support of this, all patients were terminally cyanotic, and in Cases 2 and 3 the bronchial arteries were dilated. Whether this back pressure may enlarge the septal defect is not known.

Summary

Three cases of defect of the interatrial septum with massive pulmonary thrombosis, in addition to 3 already described in the literature, are reported. A brief discussion of the hemodynamics and possible cause-and-effect relations is presented.

Massive pulmonary-artery thrombosis is a rare complication of septal defect. It is possible that the defect eventually predisposes the pulmonary artery to the formation of the thrombus, but it may also provide the mechanism for survival after an obliterating thrombosis has developed. One patient lived to be seventy-eight years of age.

References

1. Wahl, H. R., and Gard, R. L. Aneurysm of pulmonary artery. *Surg., Gynec. & Obst.* **52**:1129-1135, 1931.
2. Means, J. H., and Mallory, T. B. Total occlusion of right branch of pulmonary artery by organized thrombus. *Ann. Int. Med.* **5**: 417-427, 1931.
3. Fowler, W. M. Obliterating thrombosis of pulmonary arteries. *Ann. Int. Med.* **7**:1101-1116, 1934.
4. Kampmeier, R. H. Thrombosis of main branches of pulmonary artery, with report of case and review of literature. *J. Thoracic Surg.* **3**:513-524, 1934.
5. Pou, J. F., and Charr, R. Thrombosis of pulmonary artery: clinico-pathological study of 6 cases. *Am. Rev. Tuberc.* **37**:394-409, 1938.
6. Barsoum, H. Thrombosis of pulmonary artery. *Brit. M. J.* **2**:620, 1938.
7. Savacool, J. W., and Charr, R. Thrombosis of pulmonary artery. *Am. Rev. Tuberc.* **44**:42-57, 1941.
8. Carroll, D. Chronic obstruction of major pulmonary arteries. *Am. J. Med.* **9**:175-185, 1950.
9. Costa, A. Studio sulla morfogenesi e la fisiopatologica dei difetti congeniti del setto interatriale del cuore. *Cuore e circolaz.* **15**: 263-306, 1931.
10. Cunningham, G. J. Trilocular heart with bilateral aneurysmal dilatation of pulmonary arteries. *J. Path. & Bact.* **60**:379-386, 1948.
11. Löwenstein, K. Über Thromboarteriitis pulmonalis. *Frankfurt. Ztschr. f. Path.* **27**:226-236, 1922.
12. Lukl, P., and Benesová, D. Thrombosis of pulmonary artery and open foramen ovale. *Casop. lék. cesk.* **79**:503 and 529, 1940.
13. Burdett, J. B., and White, P. D. Large interauricular septal defect with particular reference to diagnosis and longevity: report of 2 cases. *Am. J. M. Sc.* **209**(N.S.): 355-364, 1945.
14. Taussig, H. *Congenital Malformations of the Heart.* 618 pp. New York: Commonwealth Fund, 1947.
15. Case Records of the Massachusetts General Hospital (Case 38111). *New Eng. J. Med.* **246**:419-424, 1952.
16. Roesler, H. Interatrial septal defect. *Arch. Int. Med.* **54**:339-380, 1934.
17. Dry, T. J. Atrial septal defects. *M. Clin. North America* **32**: 895-910, 1948.
18. Bedford, D. E., Papp, C., and Parkinson, J. Atrial septal defect. *Brit. M. J.* **3**:37-68, 1941.

19. Cosby, R. S., and Griffith, G. C. Interatrial septal defect. *Am. Heart J.* **38**:80-89, 1949.
20. Brannon, E. S., Weens, H. S., and Warren, J. V. Atrial septal defect: study of hemodynamics by technique of right heart catheterization. *Am. J. M. Sc.* **210** (N. S.) 480-491, 1945.
21. Westermark, N. On roentgen diagnosis of lung embolism. *Acta radiol.* **19**:357-372, 1938.
22. Hanelin, J., and Eyler, W. R. Pulmonary artery thrombosis: roentgen manifestations. *Radiology* **56**:689-702, 1951.
23. Selzer, A., and Lewis, A. E. Occurrence of chronic cyanosis in cases of atrial septal defect. *Am. J. M. Sc.* **218**(N.S.):516-524, 1949.
24. Myers, G. S. Unpublished data.
25. Lutembacher, R. Endocardite subaiguë et endartérite pulmonaire chez les cardiaques. *Arch. d. mal. du coeur* **10**:353-385, 1917.
26. Parker, Frederick, Jr., and Weiss, S. Nature and significance of structural changes in lungs in mitral stenosis. *Am. J. Path.* **12**: 573-598, 1936.
27. Edwards, J. E. Structural changes of pulmonary vascular bed and their functional significance in congenital cardiac disease. *Proc. Inst. Med. Chicago* **18**:134-146, 1950.
28. Liebermeister, H. Über Thrombose der Arteria pulmonalis. *München. med. Wchnschr.* **84**:1131, 1937.
29. Edwards, J. E., and Chamberlin, W. B., Jr. Pathology of the pulmonary vascular tree. III. Structure of intrapulmonary arteries in cor triloculare biatriatum with subaortic stenosis. *Circulation* **3**:524-530, 1951.
30. Massee, J. C. Atrial septal defect: correlation of autopsy findings with data obtained by right heart catheterization. *Am. J. M. Sc.* **214**(N.S.):248-251, 1947.
31. Welch, K. J., and Kinney, T. D. Effect of patent ductus arteriosus and interauricular and interventricular septal defects on development of pulmonary vascular lesions. *Am. J. Path.* **24**:729-756, 1948.
32. Brecher, G. A., and Opdyke, D. F. Relief of acute right ventricular strain by production of interatrial septal defect. *Circulation* **4**: 496-502, 1951.

GYNECOMASTIA DURING DIGITALIS THERAPY*

Report of Eight Additional Cases with Liver-Function Studies

EDWARD B. LEWINN, M.D.†

PHILADELPHIA

IN an earlier report[1] 6 male patients with breast changes that were interpreted as representing true gynecomastia were described. These men were receiving digitalis in various forms for the management of congestive heart failure. The structural similarity of the digitalis aglycones to the cyclopentanoperhydrophenanthrene radical of the steroidal hormones (Fig. 1) raised the question whether digitalis was itself responsible for the breast changes or whether hepatic insufficiency incident to myocardial failure or nutritional factors might have been the underlying causes.

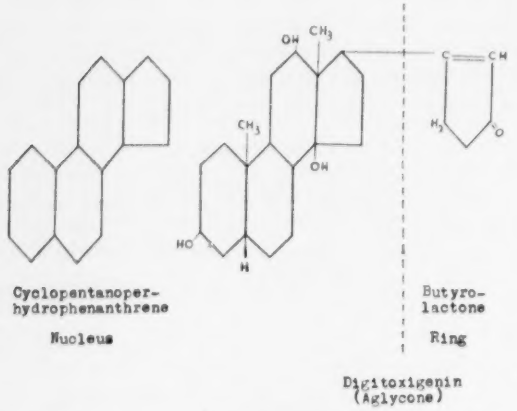


FIGURE 1. *Structure of Cyclopentanoperhydrophenanthrene Compared with That of the Digitalis Aglycones.*

In the present communication 8 additional cases are reported, making a total of 14 cases. In addition, the results of various studies made in an effort to clarify the cause of gynecomastia in 7 of these patients are presented. In general the breast manifestations in these men, as in those observed previously, consisted of the following: pain, associated with a disk-like swelling; subsidence of these symptoms and signs in 5 patients when digitalis was discontinued and their recurrence when administration was resumed; and gradual diminution of the breast enlargement after several months of continued digitalis therapy.

The ages of the entire group of 14 patients ranged from fifty-three to seventy-seven years, 4 men being fifty-three to fifty-eight, 4 being sixty to sixty-six, and 6 being seventy-two to seventy-seven years. The indication for digitalis therapy was in all cases myocardial insufficiency, the underlying cause being hypertensive heart disease in 6 cases, arteriosclerotic heart disease in 6 and chronic cor pulmonale associated with bronchiectasis and pulmonary fibrosis in 2. The forms of digitalis employed included digitoxin (0.1 to 0.3 mg. daily) in 10 cases, lanatoside C (0.5 mg. daily) in 2 cases and powdered digitalis leaf (0.06 to 0.2 gm. daily) in 2 cases. No correlation could be established between the size of dose, the type of digitalis preparation used and the duration of therapy on the one hand and the degree of breast involvement on the other. None of the 14 men received steroidal substances of any type at any time.

Histologic studies of the breast were obtained in 2 cases.

CASE REPORTS

J. M., a 61-year-old man (Table 1), who had been under constant observation and treatment for hypertension for 5 years, was first seen in March, 1947, when he suffered a left hemiplegia due to cerebral thrombosis. At that time there was an associated arteriolar nephrosclerosis. The patient's course was uneventful until June 4, 1951, when an acute posterior myocardial infarction, with pulmonary edema of moderate severity, occurred. Digitalis therapy (0.2 mg. of

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digitoxin daily) was begun and was continued until the patient's death on March 8, 1952. Once the pulmonary edema was controlled, there was no further clinical evidence of myocardial failure until November 15, 1951, when he complained of great dyspnea during an episode of auricular paroxysmal tachycardia. On August 14 a moderate, nontender enlargement of the right breast was found during routine examination. By August 30 the breast was visibly and palpably enlarged, the thickened and tender areolar disk measured 6 cm. in diameter, and the patient complained that the soreness of the breast made the pressure of his clothing almost intolerable. On that date the left breast showed a slight, nontender enlargement, which persisted without change until death. The considerable swelling of the right breast continued unabated until October 20, when the tenderness was found to have decreased to a marked degree, although there was no reduction in breast size. On December 7 digitalis was discontinued for 4 days because of nausea and vomiting. The dose on resumption of medication was 0.1 mg. of digitoxin. On December 15 the right breast first showed a decrease in size, and it continued to shrink until January 23, 1952, when only a definitely thickened, nontender areolar disk similar to that in the left breast remained.

On February 2, after a serious emotional crisis in his family, the patient's condition began to deteriorate rapidly, and he was admitted to the hospital in myocardial failure, with bilateral hydrothorax and uremia. He progressively failed in spite of all therapeutic measures, dying on March 8. The significant findings at post-mortem examination in connection with the gynecomastia were in the liver and the breasts. The former weighed 1600 gm. in air and 70 gm. in water. Its external surface was unremarkable; the cut surface was hemorrhagic. Histologic examination disclosed central dilatation of the sinusoids and atrophy of the surrounding cells. On gross examination, the left breast appeared to show slight thickening, whereas the right breast was considered normal. On microscopical section both breasts exhibited much more tissue than is normally seen in patients of similar age (Fig. 2).

TABLE 1. *Liver-Function Studies and Magnesium Sulfate Circulation Time.*

PATIENT	CIRCULATION TIME	BROMSULFALEIN RETENTION	SERUM BILIRUBIN	THYMOL TURBIDITY	SERUM CHOLESTEROL	
					TOTAL	ESTERS
	sec.	%	*mg./100 cc.*	*units*	*mg./100 cc.*	*mg./100 cc.*
R. H.	27	8	0.1	1	207	36
C. H.	18	< 4	0.6	2	282	74
F. W.	19	6	0.3	2	250	44
A. F.	18	< 4	0.5	2	215	40
J. M.	27	6	0.2	2	263	46
H. F.	—	< 4	0.2	1	124	42
J. H.	—	12	0.3	3	224	40

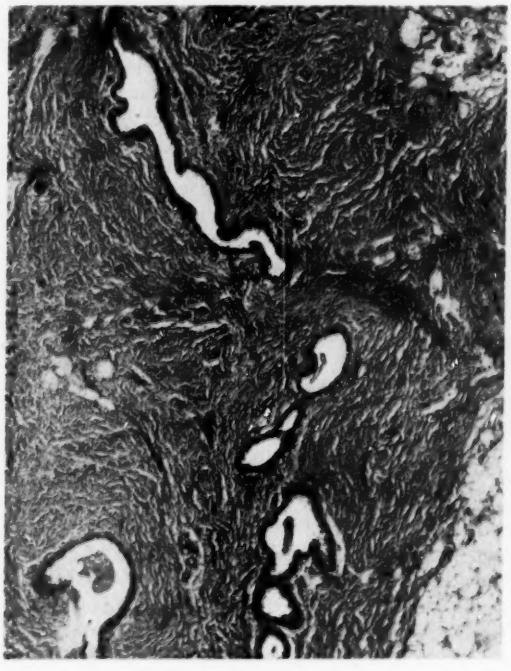

FIGURE 2. *Section of the Left Breast in Patient J. M., Showing an Increase in the Number of Ducts and of the Periductal Stroma (X75).*

Proliferation of the ductal epithelium is also seen.

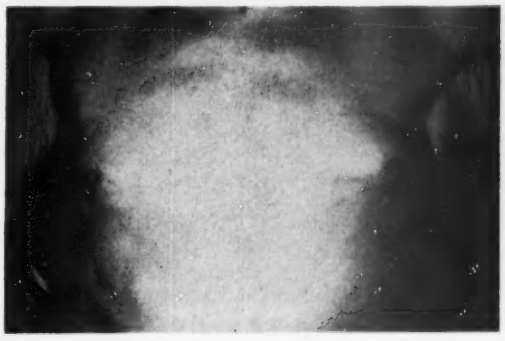

FIGURE 3. *Enlargement of the Left Breast in Patient H. F.*

H. F., a 77-year-old man (Table 1) was admitted to the hospital on April 27, 1951, complaining of substernal burning after meals, marked weakness and dyspnea. Diagnoses established during his stay in the hospital included gastric herniation through the esophageal hiatus, prolapsed internal hemorrhoids, diverticulosis of the colon, osteoarthritis of the cervical spine, prostatic hypertrophy, arteriosclerotic heart disease with a minor degree of auriculoventricular block and right-bundle-branch block and a profound anemia (hemoglobin of 4 gm. per 100 cc., red-cell count of 1,840,000, and white-cell count of 6350, with 88 per cent neutrophils and 12 per cent lymphocytes). The anemia was definitely not primary pernicious anemia, but was of the hypochromic, normocytic type and responded well to transfusions of whole blood (a total of 2550 cc.) and crude liver extract and cyanocobalamin. The cause of the anemia was not established but

was attributed to the gastric herniation. Liver-function studies were not made during this admission.

Pertinent to the question of gynecomastia were the absence of any record of breast enlargement, the lack of clinical or x-ray evidence of myocardial failure (although radiographic study showed that the heart was enlarged) and the fact that the patient had never received digitalis in any form. Shortly after discharge from the hospital on June 25, his family physician started digitoxin administration in a daily dose of 0.1 to 0.2 mg. because of persistent dyspnea. This medication was continued without interruption until the patient was readmitted to the hospital on May 28, 1952, because of cough, shortness of breath and substernal pain.

Physical examination showed pallor, auricular fibrillation, fine, crepitant rales at the bases of both lungs and a soft, slightly tender liver edge about 2.5 cm. below the right costal margin. Two observers noted independently that the left breast was visibly enlarged and quite tender (Fig. 3). The patient and his family physician were unaware of the breast enlargement until it was called to their attention in the hospital.

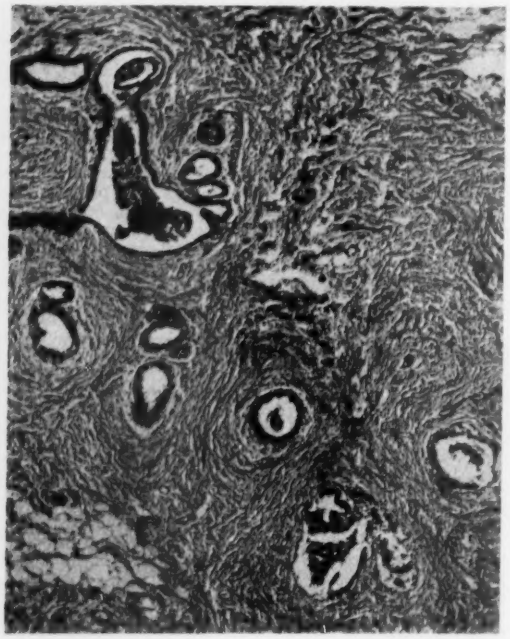

FIGURE 4. *Section of the Left Breast in Patient H. F., Showing Fibroadenomatous Hyperplasia (X75).*

Laboratory studies revealed that the blood count had again fallen but not to the levels seen on the previous admission — the red-cell count was 3,310,000, with a hemoglobin of 7.6 gm. per 100 cc., and the white-cell count 5650, with 82 per cent neutrophils, 1 per cent eosinophils and 17 per cent lymphocytes. X-ray study of the chest disclosed the same cardiac enlargement as before, segmental pneumonitis at the base of the left lung and absence of evidence of congestive heart failure. The diaphragmatic hernia was unchanged. An electrocardiogram showed auricular fibrillation, right-bundle-branch block and digitalis effects. Liver-function studies were negative except for the low level of cholesterol esters (Table 1).

The left breast was excised. On histologic examination a striking fibroadenomatous hyperplasia (Fig. 4) was seen.

Hepatic Function

In 7 cases hepatic function was studied by means of bromsulfalein excretion, thymol turbidity, serum bilirubin and cholesterol and cholesterol-ester determination (Table 1). A 5-mg. dose of bromsulfalein per kilogram of body weight was employed, and blood samples were obtained forty-five minutes after the dye had been injected intravenously. Three patients showed less than 4 per cent retention, 3 had levels between 5.5 and 8 per cent, and 1 a level of 12 per cent. It appears that 4 of the 7 patients had minimal to moderate degrees of impairment of hepatic function as indicated by the bromsulfalein test.

The serum bilirubin level was within normal limits in all patients, being 0.1 mg. per 100 cc. in 1 case, 0.2 mg. in 2 cases, 0.3 mg. in 2 cases, 0.5 mg. in 1 case and 0.6 mg. in 1 case. Similarly, the thymol turbidity was normal, a reading of 1 unit having been obtained in 3 patients, 2 units in 3 and 3 units in 1.

The total serum cholesterol was within the generally accepted limits of normal in 5 cases, ranging from 215 to 263 mg. per 100 cc. In 1 case the level was 124 mg. and in another 282 mg. per 100 cc. Of considerable interest is the fact that the cholesterol esters in all but 1 patient ranged between 36 and 46 per cent of the total cholesterol. The one exception was a level of 74 per cent in the patient whose total cholesterol was 282 mg. per 100 cc.

The circulation time was studied by the magnesium sulfate method in 5 patients.[2] Arm-to-tongue periods were 18 seconds in 2 cases, 19 seconds in 1 case and 27 seconds in 2 cases. It is noteworthy that none of these patients presented evidence of congestive heart failure on physical examination when the circulation time was determined.

Discussion

From the data presented it appears that some degree of impairment of hepatic function was present in 4 of the 7 cases on the basis of the bromsulfalein excretion and in 6 of the 7 cases on the basis of the low cholesterol-ester levels. It should be pointed out that these studies were not made until unquestionable breast enlargement had appeared and when there was no gross clinical evidence of congestive heart failure. It is also important to emphasize once more the fact that gynecomastia developed only after prolonged digitalis medication and when compensation seemed to have been reestablished. It seems reasonable to conclude that, in spite of clinical appearances, some degree of myocardial failure was present in these patients and that the depressed hepatic function was due to passive congestion of the liver. Since the liver has been implicated in many of the gynecomastias reported by other observers, it might appear that it was similarly responsible in the present group of men. However, there arise questions of considerable significance. Why was gynecomastia not present before digitalization, when cardiac failure

was most marked and liver congestion most severe? Why did the breasts become enlarged only after weeks or months of digitalis therapy and when the patients' circulatory status showed great clinical improvement?

Although a great deal of investigation will be required to clarify these questions, it is pertinent at this point to review some of the available information concerning the chemistry and the excretion of digitalis in man. The cardiotonic glycosides all contain the cyclopentanoperhydrophenanthrene nucleus (genin or aglycone) in common with the steroidal hormones, cholesterol and the vitamins D.[3, 4] At the C_{17} position is attached an unsaturated butyrolactone ring in which the cardiotonic properties of the various glycosides reside.[3, 5] The aglycones differ from each other in the stereochemical relation of their ring structures and in the number of hydroxyl groups attached to the rings. The aglycones greatly enhance the cardiotonic activity of the lactone ring, and variations in their structure modify that activity quantitatively.[6, 7]

The fate of the digitalis glycosides in the body is as yet a controversial subject. Whereas Hanzlik and Wood[5] state that digitalis cannot be isolated from the urine, Friedman et al.[8] have shown that digitoxin is excreted by the human kidney at a rate dependent on the age of the subject, the method of administration and the quantity given. Solomon[9] concluded that some digitalis is excreted by way of the kidneys and some by way of the bile, by means of which it appears in the feces. However, the recent report of Okita and his associates,[10] although based on only 3 patients with cardiac failure, is most interesting. Using highly purified radioactive digitoxin, administered intravenously, these observers found that the major route of excretion of digitoxin in man is through the kidneys and not via the liver and gastrointestinal tract, 60 to 80 per cent of the drug being eliminated in the urine either as unchanged digitoxin (6 to 10 per cent) or as its chloroform or water-soluble metabolites (52 to 72 per cent). Of further interest is the fact that unchanged digitoxin was detected in the urine for twenty-three to fifty days, whereas the metabolites were excreted in thirty-one to eighty-five days.

Of major concern in the present report are the metabolites, particularly the chloroform-soluble fraction, about whose chemistry little or no information is as yet available. However, it is probable that they consist essentially of the aglycone portion of the digitalis glycoside. It seems reasonable to conclude that these phenanthrene derivatives, like the steroidal hormones, undergo modification and possibly esterification in the liver before being excreted in the urine. In such circumstances, impairment of hepatic function, which, as is well known, is often accompanied by gynecomastia, may intensify any estrogen-like effect that the digitalis steroids possess.

It is important to consider the age of the men in the present report. The youngest was fifty-three years, and the oldest seventy-seven years. Several factors must be noted in this connection, the first being the probable relative lack of androgens, both adrenal and testicular, in these patients as compared with younger men. This would serve to enhance any estrogenic activity of the digitalis aglycones. Moreover, if estrogenic secretion by the adrenal cortex were commonly of sufficient magnitude, one should expect gynecomastia to occur with considerable frequency in men over sixty years of age, or hyperplasia of the breasts to appear more often in elderly than in younger men. However, of Geschickter's[11] series of 108 cases of gynecomastia 38 were thirteen to twenty-five, 40 were thirty to forty-five years, and 15 were sixty to seventy years old. Cheatle and Cutler[12] comment on the greater frequency of gynecomastia in the young. Only a small minority of the group of 162 patients described by Deaver and McFarland[13] and of Erdheim's[14] 12 patients were over sixty years of age. Finally, the excretion rate of digitalis is slower in persons over sixty years of age than in younger people.[6]

Summary

Fourteen cases of gynecomastia, occurring during digitalis therapy in men between the ages of fifty-three and seventy-seven years, are reported.

Liver-function studies in 7 patients indicate the presence of minimal to moderate degrees of impaired function in 4 cases, as shown by the bromsulfalein excretion test, and in 6 cases as revealed by low cholesterol esters.

The circulation time, as determined by the magnesium sulfate method, was prolonged in all 5 cases in which it was measured, although clinical evidence of congestive heart failure was lacking.

Histologic study of the breast in 2 cases showed the presence of a greater amount of tissue than is normally seen in the breasts of aged men, with striking fibroadenomatous hyperplasia in one case.

The chemical structure and the excretion of the digitalis glycosides are discussed.

The possible estrogenic activity of the digitalis aglycones is considered.

I am indebted to Drs. Henry Brody, John Robertson and Irving Young for their assistance in the selection of histologic material and to Dr. Daniel Shaw, of Wyeth, Incorporated, for his interest and co-operation.

References

1. LeWinn, E. B. Gynecomastia during digitalis therapy. *Clin. Proc. Jewish Hosp. (Philadelphia)* **4**:123, 1950.
2. Bernstein, M., Le Winn, E. B., and Simkins, S. Heart disease and liver function. *J. Lab. & Clin. Med.* **28**:1-7, 1942.
3. Oldham, F. K., Kelsey, F. E., and Geiling, E. M. K. *Essentials of Pharmacology.* 440 pp. Philadelphia: Lippincott, 1947. P. 164.
4. Burger, A. *Medicinal Chemistry.* Vol. I. 577 pp. New York: Interscience Publishers, 1951. P. 225.

5. Hanzlik, P. J., and Wood, D. A. Mechanism of digitalis-emesis in pigeons. *J. Pharmacol. & Exper. Therap.* **37**:67-100, 1929.
6. Giarman, N. J. Antibiotic lactones and synthetic analogs. II. Cardiotonic effects on isolated frog heart. *J. Pharmacol. & Exper. Therap.* **96**:119, 1949.
7. Krantz, J. C., Jr., and Carr, C. J. *Pharmacologic Principles of Medical Practice.* 1116 pp. Baltimore: Williams and Wilkins, 1951. P. 788.
8. Friedman, M., Bine, R., Jr., and Byers, S. O. Quantitative study of renal excretion of digitoxin in normal and cardiac subject. *J. Clin. Investigation* **29**:813, 1950.
9. Solomon, C. *Pharmacology: Materia medica and therapeutics.* Fifth edition. 823 pp. Philadelphia: Lippincott, 1943. P. 375.
10. Okita, G. T., Kelsey, F. E., Talso, P. J., Smith, L. B., and Geiling, E. M. K. Renal excretion of radioactive digitoxin in human subjects with cardiac failure. *Federation Proc.* **11**:380, 1952.
11. Geschickter, C. F. *Diseases of the Breast.* Second edition. 826 pp. Philadelphia: Lippincott, 1945. P. 120.
12. Cheatle, G. L., and Cutler, M. *Tumours of the Breast: Their pathology, symptoms, diagnosis and treatment.* 596 pp. Philadelphia: Lippincott, 1931. P. 58.
13. Deaver and McFarland. Cited by Cheatle and Cutler.[12]
14. Erdheim, S. Über Gynäkomastie. *Deutsche Ztschr. f. Chir.* **208**: 181-225, 1928.

ACUTE REGIONAL ENTERITIS IN CHILDREN

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BOTH the acute and chronic forms of regional enteritis have been well known pathologic entities in adults for the past twenty years. However, surprisingly little has been written about either form of the disease occurring in children.

Crohn, Ginzburg and Oppenheimer[1] presented the original description of regional enteritis in 1932, including both the acute and chronic forms. They reported 14 cases of chronic regional enteritis. The youngest patient in this series was seventeen years old. In a later paper, Crohn[2] reported 11 cases of acute terminal ileitis and stated that he had not seen a case of the disease occurring under the age of fifteen years.

Shapiro,[3] in a comprehensive review of the literature on regional enteritis published in 1939, collected 393 cases, of which 4.7 per cent occurred between the ages of one and ten years and 17.8 per cent between the ages of eleven and twenty years. Most of the patients in the latter group were over fourteen years of age. In 1941 Donald and Brown,[4] reviewing 178 cases seen at the Mayo Clinic between 1922 and 1940, reported 3 cases occurring under ten years of age and 18 cases between ten and nineteen years.

TABLE 1. *Summary of 25 Cases of Acute and 3 Cases of Chronic Regional Enteritis Occurring in Childhood, As Reported in the Literature.*

AUTHOR	AGE yr.	LOCATION	TYPE	OPERATION	FOLLOW-UP PERIOD
Rockey[5]	5	Terminal ileum	Acute	Laparotomy & appendectomy	5½ yr.
	9	Terminal ileum	Acute	Laparotomy & appendectomy	2½ yr.
	11	Terminal ileum	Acute	Laparotomy & appendectomy	15 mo.
Eckel & Ogilvie[6]	4	Ileum	Acute	Laparotomy	None
Oleson[7]	14	Ileum & cecum	Chronic	1. Ileocolostomy 2. Resection	21 mo.
Ware & Coffey[8]	8	Ileum	Acute	Laparotomy	3 mo.
Felsen[9]	5	Terminal ileum	Acute	Laparotomy & appendectomy	None
	7	Terminal ileum	Acute	Laparotomy & appendectomy	None
Eliason & Johnson[10]	13	Ileum	Acute	Laparotomy & appendectomy	2½ yr.
	5	Ileum	Acute	Laparotomy & appendectomy	2 yr.
	12	Ileum	Acute	Laparotomy & appendectomy	3 mo.
Sneierson & Ryan[11]	4	Ileum	Acute	Laparotomy & appendectomy	2 yr.
Holman[12]	6	Terminal ileum & colon	Acute	Resection	14 days
Erb & Farmer[13]	2½	Terminal ileum, cecum & ascending colon	Acute	None	Patient died (post-mortem examination)
	3	Terminal ileum & colon	Acute	Laparotomy	Patient died
	8	Terminal ileum	Acute	Laparotomy & appendectomy	None
	10	Terminal ileum	Acute	Laparotomy & appendectomy	None
Koster et al.[14]	7	Ileum	Acute	Laparotomy & appendectomy	1 yr.
Harris[15]	5	Ileum	Acute	Resection (3 ft. of ileum)	7 mo.
Garcia & Diaz[16]	9	Terminal ileum & cecum	Acute	Laparotomy	3 wk.
	11	Terminal ileum	Acute	Laparotomy & appendectomy	Patient died (post-mortem examination)
	10	Terminal ileum	Acute	Laparotomy & appendectomy	3 wk.
	10	Terminal ileum	Acute	Laparotomy & appendectomy	1 mo.
	12	Terminal ileum	Acute	Laparotomy & appendectomy	2 mo.
Bockus[17]	12	Terminal ileum & proximal ⅓ of colon	Chronic	Ileocolostomy	4 yr.
Ebrill[18]	9	Ileum	Acute	1. Laparotomy & appendectomy 2. Resection 3 wk. later for obstruction	2¼ yr.
Koop et al.[19]	0 (newborn infant)	Entire large & small bowel	Chronic	Laparotomy	Patient died at 3½ wk. of age (post-mortem examination)
O'Callaghan[20]	9	Ileum	Acute	Laparotomy & appendectomy	2 yr.

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We have been able to find only 25 cases of acute regional enteritis and 3 cases of chronic regional enteritis reported in children from birth to fourteen years of age (Table 1). Of the 25 patients with the acute form, those who survived the acute episode remained asymptomatic for the follow-up period listed. None of these cases had been observed longer than two and a half years after the diagnosis of acute regional enteritis was made, with the exception of Rockey's[5] first case, which was followed for five and a half years. Therefore, one cannot safely say that the patient had not gone on or will not go on to the chronic form of the disease.

Numerous authors[4, 6, 7, 21-23] have suggested that spontaneous recovery from acute regional enteritis, without progression to the chronic stage, occurs in a high percentage of cases, although, as Ware and Coffey[8] have stated, "a true picture of the ultimate outcome of (acute regional enteritis) cases depends on long and careful follow-up studies." It is the purpose of this paper to present such a study.

TABLE 2. *Summary of 8 Cases of Acute Regional Enteritis (Mary Hitchcock Memorial Hospital, 1939 to 1952).*

PATIENT	SEX	AGE AT ONSET	PREVIOUS SYMPTOMS	FINDINGS AT OPERATION	FOLLOW-UP STUDY	
					DURATION	RESULT
		yr.				
P. G.	F	5	None	Normal appendix; terminal ileitis (3-4 cm.).	3 mo.	Negative barium-enema examination
T. C.	F	6	Epigastric pain with nausea and vomiting 1 mo. preoperatively	Terminal ileitis involving cecum and appendix	3 yr.	Negative gastrointestinal series 7 wk. and negative barium-enema examination 3 yr. postoperatively
I. B.	F	2	None	Terminal ileitis (8 cm.) involving medial portion of cecum and appendix	4 yr.	Negative barium enemas 6 wk. & 4 yr. postoperatively
H. R.	F	7	None	Normal appendix; terminal ileitis (10 cm.).	8 yr.	
W. H.	M	4	None	Normal appendix; terminal ileitis (8-10 cm.).	12 yr.	Negative gastrointestinal series 9 yr. postoperatively
J. S.	M	11	None	Normal appendix; terminal ileitis (61 cm.).	12 yr.	Negative barium-enema examination 12 yr. postoperatively
S. S.	F	5	None	Normal appendix; terminal ileitis (6 cm.).	12 yr.	Negative barium-enema examination 12 yr. postoperatively
L. W.	M	9	None	Normal appendix; terminal ileitis (4 cm.), with ileocecal valve and ⅓ of cecum involved.	13 yr.	

CLINICAL MATERIAL

From 1939 to 1952, 8 patients with acute regional enteritis were admitted to the Pediatric Service of the Mary Hitchcock Memorial Hospital (Table 2).

All these cases presented a picture simulating acute appendicitis. There was no history to suggest intussusception in any. All had an exploratory laparotomy and appendectomy performed. A small amount of free peritoneal fluid and the presence of a mild to moderate degree of mesenteric adenitis were noted in each case. The gross appearance of the terminal ileum in each of these cases led the surgeon to make a diagnosis of terminal ileitis. The features indicating that diagnosis were engorgement, thickening and relative rigidity of the involved segment of bowel. In one case, P. G., the terminal ileum was biopsied and showed an acute ileitis microscopically. In no patient was a segment of the bowel removed, nor were hormone preparations used in medication. All had negative skin reactions to tuberculin.

The period of follow-up ranged from three years to thirteen years in 7 cases. P. G., our most recent patient, has been observed for only three months since her operation. All patients have been completely free of symptoms referable to the gastrointestinal tract, and in 6 x-ray study has given no evidence of disease. We were unable to obtain follow-up x-ray films in 2 cases (H. R. and L. W.).

DISCUSSION

This series is admittedly small, but the follow-up study on these patients suggests that acute regional enteritis, for the most part, is a nonrecurring process in children, with rare progression to the chronic stage of the disease. Our experience with the disease has led us to agree with Bargan[24] that in children, "acute regional enteritis and chronic regional enteritis are not the same entity."

The history in our 8 cases did not suggest appendiceal dysentery[9] — that is, there was no associated diarrhea, either manifest in the patients or within their families or communities. Therefore, stool cultures were not obtained before or after operation. The culture taken from within the terminal ileum at the time of biopsy in patient P. G. was negative for pathogens. The first 5 patients in the series received no antibiotics postoperatively and responded as well as the last 3, in whom antibiotic therapy was instituted immediately after operation.

Felsen's[9] work on appendiceal dysentery (normal appendix, mesenteric adenitis and terminal ileitis),

in which he isolated either Sonne–Duval (*Shigella dysenteriae*) or Flexner type of bacilli (*S. paradysenteriae*) from the stools of 12 patients with this triad, is unique. It represents the only series of cases of regional enteritis on record in which an etiologic agent has been demonstrated.

Most authors agree that the treatment of acute regional enteritis, in both children and adults, should be conservative: exploratory laparotomy with or without appendectomy. There is disagreement about the advisability of appendectomy in these cases. The main objection has been the fear that a fistula will form at the site of the appendiceal stump. This point has been stressed by Ware and Coffey,[8] Hawthorne and Frobese,[25] Fallis[26, 27] and others. On the other hand, many authors,[5, 6, 10, 11, 23] including Fallis,[26, 27] have reported numerous cases of acute regional enteritis in which appendectomy was performed without untoward results. The views of those favoring appendectomy can be summarized by the comment of Eliason and Johnson[10]:

> If the appendix is not removed and the patient has recurrent pain and tenderness in the RLQ, one is constantly faced with the problem of whether it is still regional enteritis. On the other hand, if the cecum and appendix appear to be involved in the disease process, the appendix should be removed, since the edema in its wall could quickly lead to obstruction and early perforation.

Appendectomy was performed in all 8 cases. The inflammatory process involved the appendix and cecum in 2 cases, and the ileum was biopsied in 1. All patients recovered without fistula formation. Drains were not employed. It is not our intention to suggest the correct surgical management of these cases, but only to present the various views on the subject and our own experience with this problem.

The surgical treatment of chronic regional enteritis is also a debatable subject. Garlock[23] and Hawthorne and Frobese[25] are of the opinion that the treatment of choice is ileocolostomy, with exclusion of the involved portion of bowel. On the other hand, Kiefer et al.[28] tend more toward resection of the involved portion.

Certain patients with chronic regional enteritis — such as those with extensive involvement of the ileum and colon and those with recurrent symptoms after previous operations — have been treated with nonspecific, supportive, medical measures.[28, 29] The principles of such medical management, as outlined by Kiefer et al.,[28] are as follows: bodily rest; adequate nutrition; reduction of intestinal activity; correction of secondary systemic effects such as anemia, dehydration and hypoproteinemia; and control of infection with various antibiotics. Some reports[30, 31] indicate that ACTH and cortisone may be useful adjuncts to the treatment of these patients.

The principles of medical management enumerated above should also be employed in cases of acute regional enteritis after exploratory laparotomy with or without appendectomy and in cases in which the diagnosis is made without operation.

Summary

In a survey of the literature 25 cases of acute regional enteritis and 3 cases of chronic regional enteritis occurring in children under fifteen years of age are reviewed.

Eight additional cases of acute regional enteritis, with follow-up studies ranging from three months to thirteen years, are presented.

The medical and surgical management of acute and chronic regional enteritis is briefly discussed.

It is suggested that acute regional enteritis in childhood is a specific entity, rather than an early stage of chronic regional enteritis.

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References

1. Crohn, B. B., Ginsburg, L., and Oppenheimer, G. D. Regional ileitis: pathologic and clinical entity. *J. A. M. A.* **99**:1323-1329, 1932.
2. Crohn, B. B. Regional ileitis. *Surg., Gynec. & Obst.* **68**:314-321, 1939.
3. Ravdin, I. S., Johnston, C. G., and Shapiro, R. Regional ileitis: summary of literature. *Am. J. M. Sc.* **198** (N.S.): 269-292, 1939.
4. Donald, C. J., Jr., and Brown, P. W. Prognosis of regional enteritis. *Proc. Staff Meet., Mayo Clin.* **16**:561-564, 1941.
5. Rockey, E. W. Thickening of terminal ileum with mesenteric adenitis in children. *Northwest M. J.* **32**:145-147, 1933.
6. Eckel, J. H., and Ogilvie, J. B. Regional enteritis: report of 21 cases. *Am. J. Surg.* **53**:345-348, 1941.
7. Oleson, D. Regional enteritis. *J. Pediat.* **40**:671-674, 1952.
8. Ware, G. W., and Coffey, R. J. Acute regional enteritis. *Clin. Proc. Child. Hosp.* **4**:163-167, 1948.
9. Felsen, J. Appendicular form of bacillary dysentery, with notes on mesenteric adenitis and inflammation of distal portion of ileum. *Am. J. Dis. Child.* **50**:661-672, 1935.
10. Eliason, E. L., and Johnson, J. Acute regional enteritis. *Internat. Clin.* **1**:123-133, 1940.
11. Sneierson, H., and Ryan, J. Regional ileitis: résumé of present knowledge and addition of 22 cases from Boome County, New York. *Am. J. Surg.* **52**:424-432, 1941.
12. Holman, E. E. Discussion of Bell, H. G. Chronic cicatrizing enteritis. *Calif. & West. Med.* **41**:239-241, 1934.
13. Erb, I. B., and Farmer, A. W. Ileocolitis: acute ileocolitis simulating appendicitis and characterized by edema of ileocecal region and mesenteric glands: its relation to "regional ileitis" or "chronic cicatrizing enteritis." *Surg., Gynec. & Obst.* **61**:6-14, 1935.
14. Koster, H., Kasman, L. P., and Sheinfeld, W. Regional ileitis. *Arch. Surg.* **32**:789-809, 1936.
15. Harris, F. I. Earliest acute stages of regional ileitis. *Arch. Pediat.* **57**:367-376, 1940.
16. Garcia, A. L., and Diaz, C. J. G. La ileitis regional aguda primitiva en los ninos. *Arch. argent. de pediat.* **19**:281, 1943.
17. Bockus, H. L. Present status of chronic regional or cicatrizing enteritis. *J. A. M. A.* **127**:449-456, 1945.
18. Ebrill, D. Case of regional enteritis in childhood. *Brit. J. Surg.* **32**: 512-514, 1945.
19. Koop, C. E., Perlingiero, J. G., and Weiss, W. Cicatrizing enterocolitis in newborn infant. *Am. J. M. Sc.* **214**:27-32, 1947.
20. O'Callaghan, R. Acute terminal ileitis. *West. J. Surg.* **60**:17-19, 1952.
21. Smithy, H. G. Conservatism in surgical management of acute regional enteritis. *Surgery* **13**:122-130, 1943.
22. Cave, H. W. Inflammatory lesions of small intestine: surgical aspects. *J. A. M. A.* **127**:456-458, 1945.
23. Garlock, J. H. Present status of problem of regional ileitis. *Am. J. Surg.* **72**:875-878, 1946.
24. Bargan, J. A. Discussion of Kiefer, E. C., and Ross, J. R. Criteria in management of chronic ileitis. *J. A. M. A.* **129**:104-108, 1945.
25. Hawthorne, H. R., and Frobese, A. S. Chronic stenosing regional enteritis: surgical pathology and experience in surgical treatment. *Ann. Surg.* **130**:233-241, 1949.
26. Fallis, L. S. Regional enteritis. *Ann. Surg.* **113**:1061, 1941.
27. *Idem.* Regional enteritis: case reports. *Am. J. Surg.* **62**:225-230, 1943.
28. Kiefer, E. D., Marshall, S. F., and Brolsma, M. P. Management of chronic regional enteritis. *Gastroenterology* **14**:118-130, 1950.
29. Dashiell, G. F., and Kirsner, J. B., Klotz, A. P., and Palmer, W. L. Regional enteritis: follow-up study of 40 cases. *M. Clin. North America* **35**:227-241, 1951.
30. Gray, S. J., Reifenstein, R. W., and Benson, J. A. ACTH therapy in ulcerative colitis and regional enteritis. *New Eng. J. Med.* **245**: 481-487, 1951.
31. Machella, T. E., and Hollan, O. R. Effect of cortisone on clinical course of chronic regional enteritis and chronic idiopathic ulcerative colitis. *Am. J. M. Sc.* **221** (N. S.): 501-507, 1951.

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PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Continued)*

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Effects of cortisone on endocrine system.

Anterior pituitary body and adrenal glands: It is well known that the administration of cortisone to animals and man leads to a suppression of endogenous adrenocortical secretion. Several lines of evidence may be cited. Patients, both male and female, with an intact pituitary-adrenal system may show a decreased urinary 17-ketosteroid output during cortisone therapy (50 to 75 mg. a day). After cortisone administration ACTH may elicit a poor adrenal response as measured by eosinophil fall, and 17-ketosteroid and formaldehydogenic steroid rise in the urine. When cortisone therapy is suddenly withdrawn clinical evidences of adrenal insufficiency, such as weakness, fatigability, hypotension and collapse, may be observed. These signs and symptoms may be accompanied by a relatively high eosinophil count and a low 17-ketosteroid and formaldehydogenic steroid excretion in the urine. Indeed, death from adrenal insufficiency has been reported under these circumstances.[190] Acute adrenal insufficiency is more commonly observed after the withdrawal of orally administered cortisone because of the abrupt decrease in hormonal levels in contrast to the more gradual decline after discontinuation of intramuscularly injected hormone. Finally, atrophy of the adrenal cortex has been repeatedly observed in both animals[191] and man[192] after the administration of cortisone (Fig. 16). This atrophy is largely confined to the fascicular and reticular layers, where there is a reduction of lipid concentration. The zona glomerulosa remains virtually unchanged.

There is strong evidence that the suppression of adrenocortical activity is secondary to the depression of the output of ACTH by the anterior pituitary body. The adrenal response to stress, as measured in animal experiments by adrenal hypertrophy and depletion of ascorbic acid and cholesterol, may be blocked by the administration of cortisone. With increasing intensity of stress, the amount of steroid required to suppress adrenocortical activity becomes correspondingly greater.[193] Furthermore, the adrenal atrophy that follows cortisone therapy may be prevented by the simultaneous injection of ACTH.[194] Finally, suggestive evidence of a direct effect on the pituitary gland has been provided by Sayers et al.,[195] who have demonstrated diminished blood levels of ACTH in patients with adrenogenital syndrome after cortisone therapy. The striking similarity of adrenocortical response to ACTH in patients with hypopituitarism and in patients with intact adrenal glands after a prolonged course of cortisone therapy is illustrated in Figure 17. The possibility remains, however, that cortisone also exerts a direct effect on the adrenal gland.

FIGURE 16. *Effect of Cortisone on the Adrenal Gland (We are Greatly Indebted to Drs. D. Feriozi and B. H. Landing, of the Department of Pathology, Children's Hospital, Boston, for Permission to Use This Illustration).*

The gland on the left was obtained from a four-year-old girl with acute leukemia who received cortisone, 100 mg. a day, for four weeks before death. The gland in the center was from a four-year-old girl with pulmonary stenosis who died during operation. The gland on the right came from a four-year-old girl with Letterer-Siwe disease who received 50 mg. of ACTH daily for three weeks before death.

Although the suppression of ACTH output by cortisone seems fairly well established, evidence of suppression of the output of other pituitary hormones is not so clear-cut. It has been suggested

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that the reduction in the ability of the thyroid gland to collect iodine observed with large doses of cortisone may in part reflect depression of thyrotrophic hormone (TSH) liberation.[196] However, no measurements of TSH blood levels under these conditions have been reported. Indeed, cytologic studies of the pituitary glands of rats treated with large doses of cortisone for a prolonged period indicate that the beta cells undergo changes comparable to those seen in animals after thyroidectomy, a finding suggestive of an increased output of TSH by the pituitary gland.[197] Sohval and Soffer[198] have reported an increase in urinary gonadotrophin excretion after cortisone administration. Information is not available on the possible effects of corti-

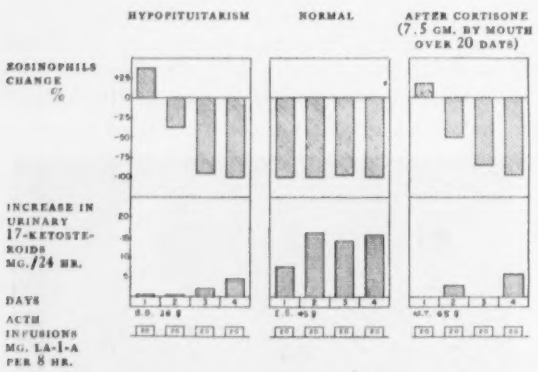
HYPOPITUITARISM
NORMAL
AFTER CORTISONE (7.5 GM. BY MOUTH OVER 20 DAYS)
EOSINOPHILS CHANGE %
INCREASE IN URINARY 17-KETOSTEROIDS MG./24 HR.
DAYS
ACTH INFUSIONS MG. LA-I-A PER 8 HR.

FIGURE 17. *Different Adrenocortical Responses to Daily Intravenous Infusions of ACTH.*
All infusions extended over eight-hour periods.

sone on the secretion of growth hormone and diabetogenic hormone.

Posterior pituitary body: No evidence of a direct action of cortisone on the posterior pituitary gland or on the release of its hormones has been reported. The effect of cortisone on the peripheral action of antidiuretic hormone is discussed above in the section on water metabolism.

Intermediary lobe of the pituitary gland: The existence of this part of the pituitary gland as a functional unit in man is yet to be established. It has been suggested, however, that the pigmentation of patients with Addison's disease may be related to hyperactivity of the intermediary lobe of the hypophysis[199] and that the lightening of the skin seen with cortisone therapy of hypoadrenalism may result from inhibition of this lobe.[200]

Thyroid gland: Clinical data indicate a definite effect of cortisone on measurements of thyroid function. Thus, Wolfson et al.[201] and Hill and his associates[202] have demonstrated a decrease in the I^{131} "accumulation gradient" in patients with normal adrenal function, or with Addison's disease, on moderate doses of cortisone (50 to 100 mg. a day). A similar effect with massive doses of cortisone (500 mg. a day) on the twenty-four-hour iodine uptake has been demonstrated by Fredrickson et al.[196] A decrease in the level of protein-bound iodine during cortisone therapy has also been observed.[201, 203]

The exact mode of action of cortisone in inhibiting iodine uptake is not clear. It appears that this effect is not due to an inhibition of TSH formation or release by the anterior pituitary body.[197] Woodbury and his co-workers[204] observed in hypophysectomized rats that the increase in I^{131} accumulation that followed the administration of TSH was partially suppressed by cortisone. It therefore appears that cortisone exerts its action, in part at least, by either a direct effect on circulating TSH or an incomplete block of the mechanism by which TSH influences iodine uptake. This view is strengthened by the finding that in hypophysectomized rats cortisone alone does not depress the accumulation of I^{131} by the thyroid gland.[204] Perry[205] and Albert et al.,[206] however, have reported that in intact rats the biologic decay of thyroidal radioiodine is not altered by cortisone, an indication that the steroid does not interfere with the influence of TSH on this measurement. It remains possible that the cortisone effect on iodine uptake by the thyroid gland reflects alterations in either iodine distribution or excretion.[206] It is well to keep in mind that although changes in measurements of thyroid function can be induced by cortisone, the relation of these measurements to thyroid hormone production may not be an absolute one. The effect of cortisone on the over-all function of the thyroid gland in terms of hormone output requires further study.

The interesting possibility also arises that cortisone aids in the peripheral utilization of thyroid hormone. Thus, Hill and his associates[202] noted a rise in basal metabolic rate in a hypothyroid patient receiving suboptimal doses of thyroid during cortisone administration. Lerman[207] also described a patient with hypothyroidism whose poor response to thyroid was markedly improved by cortisone administration. Beierwaltes et al.[208] demonstrated a calorigenic effect of cortisone in 2 patients with untreated myxedema. It is not clear whether this effect is mediated directly by the steroid or by an increase in thyroid-hormone utilization. In contrast, Wolfson et al.[201] speculated that normal thyroid function is necessary for maximum cortisone effect and that a decreased effect of continued cortisone therapy may depend on secondary depression of thyroid function. Evidence for such a supposition is, however, still tenuous.

Gonads: There is little information to indicate an effect of cortisone on gonadal structure and function in man. The occurrence of amenorrhea in women and loss of libido in men with Cushing's syndrome suggest a possible gonadal effect of the hormone. Menstrual abnormalities are sometimes seen in female patients to whom cortisone is being administered. Oligomenorrhea and irregularity of menstrual flow are the usual changes observed.

Experimental data are conflicting. Winter et al.[209] showed no significant effect of cortisone on the prostate and seminal vesicles of rats, whereas Antopol[184] noted retarded development of testes, seminal vesicles, prostate and ovaries of mature mice. Brown et al.[210] made the interesting observation that ACTH can inhibit the activity of administered gonadotrophin in hypophysectomized rats.

Pancreas: The effects of cortisone on carbohydrate metabolism and the relation of this hormone to diabetes mellitus are discussed above in the section on the intermediary metabolism of carbohydrate.

It is important to re-emphasize the relatively infrequent occurrence of a significant degree of hyperglycemia and glycosuria in nondiabetic patients receiving cortisone or ACTH therapy. Cases in which these manifestations develop are often those in which a familial tendency to diabetes is evident. After withdrawal of the hormones, hyperglycemia and glycosuria regularly disappear.[211] Even in Cushing's syndrome, overt diabetes is comparatively uncommon. Although 31 of the 33 patients described by Plotz et al.[212] exhibited diabetic glucose tolerance curves, only 9 had glycosuria, and frank diabetes was present in only 5.

Pancreatic lesions in patients with Cushing's syndrome are common. The lesions found have included fatty necrosis, carcinoma, purulent pancreatitis and pancreatic infarcts and cysts; in the few cases in which the islands of Langerhans have been carefully studied hyperplasia has been seen.[187] The changes produced in the pancreatic islet tissue of rats that had been given large doses of ACTH have been investigated by Baker.[213] Hypertrophy, hyperplasia and degranulation of the beta cells were observed. Mitotic figures were rare, and new beta cells appeared to arise chiefly by metamorphosis of the exocrine acinar cells in a manner similar to that described by Johnson[214] in partially depancreatized guinea pigs.

Becker[215] has drawn an interesting parallel between the diabetes resulting from the administration of ACTH and cortisone and the type of human diabetes characterized by retinal capillary aneurysms, Kimmelstiel–Wilson lesions in the kidney and the failure to develop ketosis in the absence of exogenous insulin. This author pointed out that persistent ketonemia or acidosis rarely develops in patients with steroid diabetes. He reported the appearance of retinal capillary aneurysms in 2 patients who were receiving ACTH intravenously for sarcoidosis. Finally, he recalled the observation[186] that renal lesions of the Kimmelstiel–Wilson type may develop in rabbits given cortisone. On the basis of these findings it is of interest to speculate that in both steroid diabetes and spontaneous diabetes characterized by capillary aneurysms a relative excess of the hyperglycemic-glycogenolytic factor of the alpha cells of the pancreas in the presence of a normal or mildly deficient supply of insulin might explain the defect of hyperglycemia and the capillary damage observed in both retina and kidney.[216]

The use of cortisone in the treatment of patients with coexisting Addison's disease and diabetes mellitus provides an illustration of the necessity for evaluating the effects of the hormone on specific metabolic functions in terms of the benefit to the total organism. For in spite of an increase in the severity of the diabetic state, reflected in a material rise in insulin requirement, as a result of the administration of maintenance doses of cortisone (12.5 to 25 mg. a day), the alleviation of the adrenal insufficiency, reflected in an increased food intake, weight gain and exercise tolerance, produces a marked improvement in the over-all physical status of the patient. Indeed, advantage is deliberately taken of the diabetogenic action of the hormone to protect these patients from the ever-present threat of hypoglycemic episodes, the net result being a considerable stabilization of the diabetes and a definite facilitation of therapeutic control.

Effects on integument. The administration of cortisone to patients with Addison's disease ordinarily produces striking changes in skin texture and color. The skin becomes perceptibly warmer, softer and less dry, reflecting, at least in part, an improvement in hydration resulting from the restoration of fluid and electrolyte balance. Recent studies carried out in this laboratory employing the Hardy reflectance spectrophotometer have provided objective evidence of the changes that may result from cortisone administration.[200] The distinguishing features of the reflectance curves in Addison's disease have been shown to be as follows: a significant lowering of the entire curve, reflecting the increased deposition of melanin and diffuse pigmentation that is a conspicuous feature of adrenal insufficiency; a depression of the curve in the near ultraviolet region, indicating the presence of "melanoid," a degradation product of melanin; and a flattening of the curve in the 450-470-millimicron area and a loss of the characteristic fluctuations due to oxyhemoglobin, a shift that is probably due to a smaller content of blood in the reflecting tissues and a relative increase in venous blood content. After the institution of maintenance cortisone acetate therapy, a generalized and progressive lightening may be demonstrated owing to a decrease in the skin content of melanin. The reduction in pigmentation, however, is far from complete as indicated by a persistence of the characteristic reflection pattern of "melanoid." A reversion of the oxyhemoglobin band toward normal undoubtedly reflects improved vascularity and hydration. Other changes encountered during substitution therapy with cortisone include an increase in hair growth in the sexual areas and on the extremities. At the dosage level ordinarily employed in the treatment of patients with Addison's disease no other changes attributable to androgenic activity have been seen.

The employment of large doses of cortisone during prolonged periods of therapy in patients with intact adrenal glands may result in striking changes in the skin, comparable to those encountered in patients with Cushing's syndrome. A generalized thinning of the skin is sometimes observed and may be accompanied by the formation of violaceous striae. The mechanisms of these changes in Cushing's syndrome have been eloquently discussed by Albright,[120] who considered the antianabolic effects of oxygenated adrenocortical steroids on protein to be responsible. A characteristic rounding of the face is often encountered, constituting an early sign of cortisone overdosage. This change in facial appearance is not necessarily correlated with the occurrence of weight gain or edema, and has usually been attributed to a local increase in fat deposition. The appearance of acne, keratosis pilaris and occasionally hirsutism during the prolonged administration of large doses of cortisone reflects the metabolic conversion of this hormone into steroids possessing definite androgenic activity. The effects of large doses of cortisone, administered both systemically and locally, on the skin of rats have been carefully studied by Baker et al.[217] Striking changes in skin structure were produced, including a thinning of the epidermis due to an absolute reduction in the number of epithelial cells, an almost complete inhibition of hair growth and an atrophy of sebaceous glands. The dermis was similarly affected, with a pronounced decrease in thickness caused by a "melting down" of collagen fibers into a compact, almost homogenous, mass, and an absolute reduction in the number of fibroblasts, with shrinkage and pyknotic changes in the nuclei of the cells that survived. Elastic fibers were apparently spared. It is of interest that inunction of cortisone over a protracted period in these animals had no systemic effects.

A careful investigation of the skin in numerous patients representing a large group of dermatoses treated with cortisone and ACTH has been carried out by Sauer and his associates.[218] The results of these studies can be summarized as follows: the absorption time of intracutaneously injected saline solution was significantly shortened; skin temperature showed a distinct tendency to elevation; sweating was augmented; sebum and other fat-soluble materials delivered at the skin surface were diminished; and examination by stereoscopic microscope revealed an enhanced blood flow. All the effects listed were interpreted as evidence of an accelerated peripheral circulation. In view of the decrease in sebum, it is of interest that Brunsting[219] has pointed out the fact that acne occurring during the administration of cortisone is not often accompanied by seborrhea.

Healing of acute inflammatory lesions of the skin during treatment with cortisone may be accompanied by the local deposition of pigment. Local pigmentation is frequently seen in the scar at the site of implantation of cortisone pellets. In contrast to ACTH, however, the administration of large quantities of cortisone over prolonged periods does not ordinarily result in a generalized darkening of the skin.

Effect on musculoskeletal system.

Muscle: Muscle weakness is a cardinal symptom of Addison's disease. Furthermore, the capacity of adrenalectomized animals to perform muscular work has served as the basis of tests proposed by Everse and De Fremery[220] and by Ingle[94] for the detection and assay of adrenocortical steroids. The latter procedure has proved of inestimable value in the comparative assay of crystalline steroids and in the elucidation of the physiologic actions of these compounds.[221] Although the advent of muscular exhaustion in the adrenalectomized animal subjected to continual muscle stimulation is apparently correlated with circulatory failure, the probability remains that 11,17-oxygenated corticosteroids are directly involved in the maintenance of metabolic processes intrinsic to muscle contraction. Cortisone has proved considerably more effective than desoxycorticosterone, corticosterone and dehydrocorticosterone in the maintenance of muscular capacity in adrenalectomized animals[221] and in patients with Addison's disease. It is of interest, however, that cortisone is definitely less effective in the Ingle work test than aqueous adrenocortical extract. On the other hand, neither adrenocortical extract nor any crystalline steroids yet available can elevate muscle work output in the adrenalectomized rat to levels characteristic of normal animals, or increase further the work capacity of normal muscle.[222]

During the administration of cortisone to patients without primary muscle disease an increase in creatine excretion is sometimes encountered. Preformed creatinine output, however, remains unchanged. In view of the studies of Zierler et al.[223] on the influence of desoxycorticosterone acetate on the mechanisms of creatine excretion, cortisone may also be capable of reducing tubular reabsorption of creatine.

Shy et al.[224] have shown that the administration of cortisone to patients exhibiting the primary muscular abnormality of myotonia may result in a significant decrease in myotonic response. Since the pharmacologic characteristics of myotonia are diametrically opposed to those of myasthenia gravis, it is difficult to reconcile this result with the improvement of neuromuscular conduction, muscle contractility and strength reported in myasthenia gravis during intensive adrenocortical stimulation.[225] Indeed, it appears that the abnormalities in neuromuscular function in myasthenia gravis are often considerably aggravated during hormone administration, with subsequent improvement above control

levels of function during the rebound period of relative adrenal insufficiency after hormone withdrawal.

During the protracted administration of large doses of cortisone muscular function and strength may become seriously impaired. It is apparent that the majority of cases result from serious potassium depletion although patients with temporary muscular weakness have been described in whom no significant loss of potassium could be demonstrated.[116] Since a decrease in muscle strength is a well recognized component of Cushing's syndrome, a prolonged interference with protein synthesis during chronic cortisone administration may be responsible in part for the impairment of muscle-fiber strength.

It is of interest, therefore, that muscular weakness may be a prominent feature of both adrenocortical-hormone deficiency and hormone excess. It appears that the mechanism most frequently responsible is a significant alteration of serum (and undoubtedly tissue) electrolyte concentrations. An extremely useful index for evaluating serum electrolyte content is the readily obtainable ratio of serum sodium to potassium.[48] A marked alteration of this ratio in either direction may well result in striking abnormalities in muscular function.

Bone and cartilage: The administration of large doses of cortisone ordinarily results in an increased output of calcium and phosphorus. Changes in calcium balance are considered to reflect chiefly alterations in bone composition. Discrepancies in the anticipated renal excretion of phosphorus, based on theoretical ratios of calcium to phosphorus and nitrogen to phosphorus in bone and protoplasm respectively, have been attributed to changes in the tubular transfer of phosphorus, and to retention in association with increased liver glycogen.

Becks et al.[226] have shown that intensive adrenocortical hypersecretion results in a derangement of the normal processes of long-bone growth in rats as evidenced by a striking reduction in width of the epiphyseal cartilage. Baker[227] has also reported a decreased proliferation of cartilage cells, an impairment of resorption and invasion by bone-marrow connective tissue and a diminished formation of new bone due to a reduction in the number of active osteoblasts. Winter and his co-workers[209] described comparable changes after prolonged cortisone administration.

Osteoporosis may result from the long-continued administration of cortisone. Albright[120] concluded from a classic study of Cushing's syndrome that an antianabolic action of oxygenated corticosteroids of the cortisone type could account for osteoporosis. A decrease in the formation of osteoid matrix, resulting from the interference with protein synthesis, is probably responsible for calcium and phosphorus loss. A direct effect on calcium excretion may accentuate the loss due to diminished calcium deposition. Reports of pathologic fractures in patients treated for long periods with cortisone[228, 229] serve to emphasize the potent effect of the hormone on bone formation.

Although the direct effects of cortisone on bone structure are recognized as being antianabolic, the following case emphasizes the importance in clinical therapy of evaluating the net effects of the hormone on a specific tissue in terms of the over-all effects of the hormone on the total organism:

A 51-year-old woman with nontropical sprue of 13 years' duration, and severe generalized osteomalacia, sustained bilateral impacted subcapital fractures of the femoral necks as a result of a fall. Owing to a complete absence of healing after 5 weeks of intensive supportive therapy, bilateral hip nailing was performed. Despite the presence of severe bone disease, the oral administration of 100 mg. of cortisone acetate a day was begun before operation and continued at this dosage level for 1 month, and at a level of 50 mg. a day thereafter. For the first time since admission to the hospital, diarrhea was controlled, and the appetite was markedly improved; the patient gained 25 pounds in weight during a 3-month period. Both fractures healed satisfactorily, and 3 months after operation no distinct fracture line was evident.

Certainly, the over-all therapeutic benefits accruing from cortisone therapy in this case overshadowed the risk of interfering with fracture repair; indeed, it appears quite probable that the anabolic consequences of increased food intake and improved gastrointestinal absorption resulting from the use of cortisone contributed significantly to a satisfactory process of healing.

Joints: One of the earliest detectable effects of an elevated adrenocortical secretion in human subjects is the reduction in potential difference between the inner surface of the synovial membrane and a reference electrode applied to the skin. In patients with active rheumatoid arthritis, the abnormally elevated potential may be reduced by 50 per cent, and sometimes to normal values, within twenty minutes of effective adrenocortical stimulation.[230] A decrease of intra-articular temperature in actively inflamed joints has been found to occur within twenty-four hours of cortisone administration.[231] In addition to suppressing inflammatory changes, cortisone has been shown to revert the chemical abnormalities of joint fluid to normal. After both systemic and intra-articular administration of cortisone, joint-fluid viscosity is elevated, reflecting an increase in concentration or polymerization of hyaluronic acid.[135] It should be noted, however, that the beneficial effect of the intra-articular injection of hydrocortisone is considerably more consistent than that of cortisone.[231]

Effects on connective tissue. Numerous observations have been made on the effects of cortisone on connective tissue and other mesenchymal derivatives.[232] Baker[227] has emphasized that all three essential components of connective tissue — cells, fibers and ground substances — are susceptible to the actions of the hormone.[227] Fibers and ground substances are derived from and dependent on

cells, damage to which may have profound effects on the structure of supporting tissues.

Large doses of cortisone delay fibroplasia, an action apparently independent of the initiating stimulus. Its capacity to inhibit the genesis of fibrils has been demonstrated in cultures of fibroblasts by Sacerdote et al.[233] The actions of the hormone on fibroelastic connective tissue have been well demonstrated by Castor and Baker[234] in a study of the effects of prolonged local application to the skin of rats. Fibroblasts were materially reduced in number, and residual cells were often shrunken. Collagenous fibers became arranged in an almost homogeneous, compact mass, as a result of which the dermis was greatly thinned. The ground substance was reduced in amount, and evidence of actual chemical alteration was obtained. Elastic fibers were apparently unaffected and therefore appeared more concentrated. In addition, all epithelial structures, including hair and sebaceous glands, underwent regression, and subcutaneous fat almost completely disappeared.

Lymphoid organs are essentially composed of parenchymal cells imbedded in a network of reticular connective tissue. The significance of the reticulum has been well stated as follows by Baker[213]:

> In a sense, the reticular connective tissue cell represents the retention in the adult body of a primitive form which possesses many potentialities for development. It may give rise to any of the various types of blood cells, phagocytes, and other cells. Therefore, what happens to it in the hyperadrenal state is of utmost importance to the well being of the body.

Intensive cortisone administration has been demonstrated to produce extensive disintegration of the reticular network, with shrunken cells containing irregular and frequently pyknotic nuclei, and fragmented reticular fibers. Furthermore, evidence for an inhibition of lymphocyte and thymocyte production has been derived from the scarcity of cells that are transitional between reticular connective-tissue cells and more mature forms, and from actual degeneration of the progenitor reticular cells themselves.[235] Evidence concerning the effects of adrenal hormones on the phagocytic activity of the reticuloendothelial system is conflicting. Gordon and Katsh[236] described an acceleration of splenic phagocytosis; Spain et al.,[237] however, noted a diminished phagocytic response in cortisone-treated animals. It appears possible, from the extensive structural changes described above, that prolonged and intensive hormone administration may well interfere with the phagocytic capacity of the reticuloendothelial system.

It appears well established by numerous studies in both animals[238, 239] and man[240] that the administration of large quantities of cortisone may delay wound healing. Delayed wound healing has also been frequently observed in patients with Cushing's syndrome. It is of particular interest that local application of cortisone to wounds effectively inhibits granulation, providing evidence for a direct action on processes of growth.[241]

The retardation of wound healing by cortisone has been shown to involve a depressant action on many phases of the healing process, including fibroplasia, vascularization and the deposition of extracellular ground substance. Although the inflammatory elements are largely suppressed, only a slight interference with epithelization has been observed. Changes described in the course of experimentally produced wounds in animals receiving large doses of cortisone have included: a delay in the appearance of edema after wounding; a thinning of the surface layer of red blood cells and fibrin and a paucity of white blood cells; a significant delay in the onset of fibroplasia and an abnormal appearance of the fibril bundles; a delay in onset of vascularization and an abnormal degree of capillary dilatation; and an over-all thinning of adjacent tissues.

Findlay and Howes[242] carried out an investigation of fundamental importance on the relation of protein nutrition and depletion to the effect of cortisone on wound healing. It was decisively demonstrated that protein depletion produced by starvation facilitated the interference with wound healing by cortisone and conversely that the administration of cortisone accentuated impairment of healing due to protein depletion. It is apparent that marked differences in the effect of adrenal steroids on wound repair between debilitated and adequately nourished patients should be taken into consideration.

Cortisone has been demonstrated to exert an inhibitory effect on the development of pericardial, pleural[243] and peritoneal[244] adhesions experimentally produced in animals with talc. A practical extension of this effect appears to be the increase in mobility produced by cortisone in patients with Dupuytren's contracture.[245] It is of interest that growth hormone, in contrast to ACTH and cortisone, enhances the granulomatous response to injurious substances.[246] This observation appears to support the hypothesis that growth hormone and adrenocortical steroids are antagonists in their action on the "inflammatory potential" of connective tissue.

Although the predominant influence of high doses of cortisone on protein metabolism is an interference with protein synthesis, it should be pointed out that this action can often be modified or even reversed during therapy as a result of the salutary effect of the hormone on appetite and improvement of protein and caloric intake. The most striking illustration of this phenomenon, of course, is found in patients with Addison's disease after the institution of cortisone therapy. A markedly improved sense of well-being and stimulation of appetite ordinarily result in a significant, often pronounced, weight gain. It is obvious that the increase in protein intake so far outweighs the potential deleterious effects on protein metabolism of the small substitution doses employed that the

net effect of the hormone is a stimulation of tissue anabolism. Similarly, in certain carefully selected patients with chronic inflammatory disease a judicious regulation of cortisone dosage may permit a sufficient stimulation of caloric and protein intake to offset materially, although indirectly, any impairment of protein formation. The final effect of cortisone on protein metabolism, and on other primary actions of the hormone, must therefore be evaluated in terms of the entire range of metabolic changes elicited.

Effects on hematopoietic system. Characteristic changes in the pattern of circulating blood cells are encountered in states of hypoadrenalism and adrenal hyperfunction. In addition to hemoconcentration, the blood of the majority of patients with Addison's disease exhibits the following abnormalities: a normochromic, normocytic anemia and a subnormal white-cell count, with an increase in the number of lymphocytes and normal to high levels of eosinophils. Although desoxycorticosterone therapy will lead to an increase in plasma volume with alleviation of the hemoconcentration, only cortisone will revert the cellular changes to normal.[48] In Cushing's syndrome eosinopenia is observed in a high percentage of cases; lymphocytopenia is encountered less frequently, whereas polycythemia is found in approximately half the cases.

The marked effects of ACTH on lymphocytes[247] and circulating eosinophils[248, 249] have stimulated numerous investigations of the action of cortisone on the hematopoietic system.

Eosinophils: A fall in the peripheral eosinophil count is now recognized as the most striking effect of cortisone on cellular constituents of the blood. The magnitude of this fall varies with dosage and the route of administration of the hormone[250, 251] and is probably proportional to the concentration of steroid attained in the blood stream. Studies indicate that the eosinopenic action of cortisone is as rapid and as effective when the hormone is administered by the oral route as when it is given intravenously. Because of slow absorption of intramuscularly injected cortisone, on the other hand, far larger doses have to be given by this route to produce an equivalent action.[116, 250] Eosinopenia may persist for a prolonged period in the presence of a high blood level of steroid.

Three main explanations are offered for the eosinopenic action of cortisone. The first attributes the effect to an inhibition of the production or release of eosinophils in the bone marrow. The second proposes that eosinophils are caused to enter and to be segregated in such organs as the spleen and the lungs. The third theory postulates that cortisone exerts a destructive influence on the eosinophils. Evidence that a bone-marrow effect may be a factor in the eosinopenia has been provided by Rosenthal et al.,[252] who during cortisone treatment of seven patients with nonhematologic diseases observed decreases in the blood eosinophil counts in all cases (64 to 100 per cent) and consistent increases in the bone-marrow eosinophil count (42 to 372 per cent). Gordon and his associates[253] have noted, however, that large doses of cortisone result in a marked decrease in the eosinophil content of bone marrow in mice. That sequestration of eosinophils may occur under the influence of cortisone has been suggested by demonstration of a significant drop in the number of the circulating eosinophils during passage through the lung.[254] No conclusive evidence for the participation of such a mechanism in the eosinopenia resulting from adrenal activation or cortisone administration has yet been presented. It has been adequately demonstrated that splenectomy in man does not alter the capacity of adrenal steroids to induce eosinopenia.[248] Padawer and Gordon[255] have presented strong evidence in support of the view that cortisone has a destructive effect on the eosinophil; they have observed progressive degenerative changes in the eosinophils in the blood and the peritoneal and pleural fluids of rats after the administration of this hormone. Furthermore, Muehrcke et al.[256] have demonstrated in vitro a fall in the eosinophil count of blood incubated for four hours in constant contact with cortisone acetate, although in very high concentration (1 mg. per 3 cc. of blood). This evidence is the more convincing since Muehrcke[257] showed that heparin would block this effect in vitro as it does also in vivo. However, the significance of these studies in relation to the actual process of eosinopenia in vivo remains to be demonstrated.

Lymphocytes: The work of Dougherty and White[247] showed a fall in the number of circulating lymphocytes after injection of ACTH and cortisone in rats, mice and rabbits. A lymphopenic action in man has been demonstrated by Hills et al.[248] and many others. This effect is transient, and with continuing administration of the hormone a gradual return to normal lymphocyte levels in the peripheral blood usually occurs. Like the eosinopenia following cortisone, the lymphopenia can be prevented by heparin in vivo.[257] One of the factors in cortisone-induced lymphopenia may be an accumulation of lymphocytes in the bone marrow as shown by Yoffey and his co-workers.[258] An in vitro destruction of these cells in the presence of adrenocortical extract has, however, been demonstrated by Feldman.[259] Heilman[260] likewise showed a necrotizing effect of cortisone on lymphocytes in tissue cultures. Baldridge and his associates,[261] however, were unable to demonstrate cytotoxic effects of this hormone on human lymphocytes in cultures of the buffy coat.

The lymphopenic effect of cortisone is not confined to the peripheral blood. Fixed lymphoid tissue, such as the thymus and lymph glands[247] and, temporarily at least, the abnormal cells of lympho-

sarcoma and chronic lymphatic leukemia,[148] are sensitive to the action of the hormone.

Neutrophils: It has been clearly demonstrated that cortisone will often produce a striking neutrophilia.[116, 262] This effect appears to be due to stimulation of the bone marrow. Indeed, myeloid hyperplasia has been observed after cortisone administration to animals.[263]

Erythrocytes: Cortisone has been shown to cause a significant reticulocytosis and an improvement of anemia in a variety of conditions such as rheumatoid arthritis and Still's disease,[262] and disseminated lupus erythematosus. Since little or no improvement of anemia has been observed when the clinical response has been poor, it is believed that the cortisone effect in these patients is dependent more on the control of the underlying disease than on a specific stimulation of the bone marrow. A reticulocytosis has been observed to follow the administration of cortisone to patients with pernicious anemia.[264] No reports of the occurrence of polycythemia in association with cortisone treatment have appeared.

Platelets: No effect of cortisone on the number of platelets or megakaryocytes has been observed in man in conditions in which there is no abnormality of these elements.[262] The hormones are ineffective in thrombocytopenic purpura when the marrow is hypoplastic, or when platelet formation has been depressed by chemical intoxication or irradiation. In states in which the thrombocytopenia is associated with normal bone marrow, particularly in idiopathic thrombocytopenic purpura, however, the administration of cortisone may cause the number of platelets in the peripheral blood to return to normal.[265] It is of interest that in these conditions the bleeding time may become normal before any change in platelet counts is observed. Similarly, cortisone may control the hemorrhagic manifestations of aplastic anemia, disseminated lupus erythematosus and leukemia, although platelet counts may not change.[266]

Blood coagulation: There is a variance of opinion about the effect of cortisone on blood coagulation. Prompted by the observation that ACTH and cortisone therapy was attended with an increased incidence of thromboembolic complications Cosgriff, Diefenbach and Vogt[267] investigated the effects of these drugs on blood coagulation. They found that cortisone, 100 mg. daily, induced a great decrease in clotting time in all 5 patients investigated, with no effect on the heparin-retarded clotting time, the prothrombin time or the circulating heparin-like substances. Similar findings were obtained by Godlowski.[267] Monto et al.,[268] on the other hand, reported that ACTH and cortisone produced a transient initial increase in clotting time and in circulating heparin-like substances, followed after twenty-four hours, in 12 out of 20 patients, by a decreased clotting time. Fahey,[269] however, observed no blood coagulation changes in patients given large doses of cortisone by both oral and intramuscular routes.

Effects on cardiovascular system.

Blood pressure: The occurrence of hypotension in patients with adrenocortical hypofunction and a high incidence of hypertension in adrenocortical hyperfunction is well known and has long stimulated speculation concerning a possible supportive role of the adrenal cortex in essential hypertension.[270] The observation that the development of Addison's disease in a patient with essential hypertension is ordinarily followed by a return of blood pressure to normotensive or even hypotensive levels directly suggests a failure of mechanisms involved in the maintenance of the hypertensive state after the loss of adrenocortical function. Recent studies of the effects of total[36] and subtotal[271] adrenalectomy in patients with hypertension are indicative of the intense interest that surrounds the important question of a possible relation between the adrenal cortex and the hypertensive state.

Numerous studies have been carried out concerning the effect of adrenalectomy in experimental hypertension[272, 273] and the relation of desoxycorticosterone to both functional[274] and structural[275] alterations in the cardiovascular system. Comparatively few reports are available, however, on the influence of cortisone on circulation. The administration of the hormone to unilaterally nephrectomized rats maintained on a high-sodium, high-protein intake has resulted in hypertension.[185] After adrenalectomy renal hypertension in the rat has been restored by the administration of cortisone.[276] In addition, hypertensive effects of cortisone have been demonstrated in nephritic (cytotoxic-serum) rats before and after adrenalectomy.[277] Although cortisone has been shown to cause a resolution of the inflammatory component of desoxycorticosterone-induced hypertensive arteritis in rats, no influence on nephrosclerosis was evident, and the onset of hypertension was somewhat accelerated.[278] It therefore appears that the capacity of cortisone to increase arterial pressure is, like that of desoxycorticosterone, accentuated in the presence of renal damage and states of adrenal insufficiency.[279] The administration of cortisone to dogs has been shown to produce a definite rise in plasma hypertensinogen levels unaccompanied by a rise in blood pressure.[280] No effect on hypertensinogen levels in human subjects could be demonstrated. The observations of Rich[186] on the development of vascular lesions in rabbits strikingly similar to nodules of the Kimmelstiel-Wilson type are described above.

The administration of cortisone alone has been demonstrated to be capable of correcting peripheral vascular failure encountered in acute adrenocortical insufficiency. For maintenance therapy, on the other hand, the majority of patients with Addison's disease require small doses of desoxycorticosterone

in addition to daily substitution doses of cortisone. A growing experience with the use of cortisone therapeutically has made it evident that the administration of moderate doses (50 to 150 mg. daily) to normal persons rarely produces a significant rise in blood pressure. Even doses as large as 300 to 500 mg. given daily by intramuscular injection or by mouth over prolonged periods have been found to cause only a slight rise in blood pressure in occasional patients. These findings are in agreement with those of Sprague et al.,[116] who observed an elevation in blood pressure in only 1 of 33 patients on long-continued cortisone or ACTH therapy. Perera[281] has emphasized the occurrence of hypertension during cortisone therapy in patients with impaired renal function, an experience that coincides with the results achieved by administration of the hormone to animals with acute renal damage.[282]

It has been observed that under certain circumstances cortisone may actually reduce blood pressure. This action has occasionally, although not consistently, been seen after administration to patients with essential hypertension.[282, 283] Similarly, both hypotensive[284] and hypertensive[278] effects of cortisone have been reported in rats made hypertensive by the administration of desoxycorticosterone acetate. That cortisone is able to counteract an elevation of blood pressure due to certain abnormal patterns of adrenocortical steroid secretion has been convincingly demonstrated by Wilkins et al.,[285] who recorded the restoration of normal blood pressures in 3 hypertensive patients with congenital adrenal hyperplasia after treatment with cortisone acetate.

Peripheral circulation: An increase in capillary resistance in human subjects treated with cortisone has been reported by Robson and Duthie.[286] Confirmatory evidence has been obtained by the intravenous infusion of T-1824 dye in wounded, cortisone-treated animals.[242] The diffusion of dye into the wounds of these animals was demonstrated to be less than that occurring in the wounds of control animals not receiving cortisone. It is of interest that Swingle[67] arrived at a similar conclusion many years ago concerning the relation of adrenal hormones to capillary permeability on the basis of infusion experiments in adrenalectomized dogs.

Recently Ramey et al[287] showed that infusion of nor-epinephrine produced a rise in blood pressure that was smaller in adrenalectomized than in normal dogs, and that the administration of adrenocortical extract (but not desoxycorticosterone) caused a significant rise in blood pressure in adrenalectomized animals receiving simultaneous intravenous infusions of nor-epinephrine. Further work by Fritz and Levine[288] demonstrated that the responsiveness of the vessels of the rat's mesoappendix to the topical application of nor-epinephrine was reduced by adrenalectomy and subsequently restored by the local application of aqueous adrenocortical extract. Desoxycorticosterone again proved inactive. Similarly, human subjects respond to nor-epinephrine and Neo-Synephrine with a brisk rise in blood pressure after complete bilateral adrenalectomy during the administration of adequate doses of cortisone acetate.

The observations of Brust, Ransohoff and Reiser[289] are of interest in relation to the possible effects of cortisone and ACTH on humoral mechanisms affecting vascular tone. The administration of cortisone to both normotensive and hypertensive subjects resulted in a significant decrease in the hypotensive response to TEAC (tetraethylammoniumchloride). With continued administration of the hormones the normal depressor effects of TEAC were eventually converted into a pressor rise. Desoxycorticosterone proved ineffective. The responses were independent of sodium retention and often preceded the maximal eosinopenic response to the hormones. These studies were considered to demonstrate that certain vascular effects of cortisone and ACTH may be mediated by an unidentified humoral mechanism that is potentiated by autonomic blockade.

The increased cutaneous blood flow and the changes in renal hemodynamics that may result from the administration of cortisone have already been described. Myers and Taylor[290] have demonstrated a significant rise in hepatic blood flow and an increase in splanchnic oxygen consumption.

The marked vascular fragility of patients with Cushing's syndrome is well known. Similar changes may be seen after the protracted administration of large quantities of cortisone. It has been suggested[120] that this alteration of vascular structure represents an additional example of the fundamental action of the hormone on protein formation.

Since cortisone may increase plasma cholesterol levels, studies of its effect on atherogenesis have been carried out. Stamler et al.[291] found a significantly greater incidence and severity of aortic and coronary atherosclerosis in cortisone-treated chicks receiving a high-cholesterol diet. Etheridge and Hoch-Ligeti[292] described an increased deposition of lipid in the intima and media of patients under eleven years of age after prolonged therapy with cortisone or ACTH. Because of the apparent correlation between the serum level of giant cholesterol-containing lipoproteins of the S_f 10–20 class with atherosclerosis in human beings, Bloom and Pierce[293] studied the effect of cortisone on these substances. After administration of the hormone for periods as long as nineteen months, however, no definite alteration in lipoprotein level could be demonstrated. It is of interest that a comparable study in rabbits revealed pronounced changes in lipoprotein pattern indicating that cortisone induced a "metabolic block" at the level of S_f 40–80 class of lipoproteins with a resultant accumulation of higher S_f molecules.[294]

Cardiac function: Few studies have been reported on the action of adrenocortical steroids on cardiac function. Perera[281] reported a slight decrease in cardiac output after cortisone in 1 hypertensive subject. Horwitz and his associates[295] also noted a mild decrease in cardiac output in normotensive patients with rheumatoid arthritis during cortisone therapy but considered the effect largely secondary to a fall in cardiac rate as a result of the improvement in inflammatory disease. Patients with Addison's disease often show nonspecific abnormalities of the electrocardiogram, such as flat or inverted T waves, a prolonged QT, PR or QS interval, low voltage and depression of the ST segment. Somerville et al.[296] demonstrated that the administration of cortisone in maintenance doses frequently results in a significant improvement, or even complete reversion, of these cardiographic abnormalities. Comparative studies of the electrocardiogram in patients with Addison's disease and Cushing's syndrome[297] described the interesting finding that the PR interval tends to be in the upper range of normal or abnormally long in adrenal insufficiency, whereas the opposite situation obtains in hypercorticism. The mechanisms by which cortisone influences the electric activity of the heart remains unknown.

Effects on gastrointestinal system. Cortisone has been shown to have the same qualitative effects as desoxycorticosterone on the electrolyte content of saliva. It causes a reduction in the sodium and an increase in the potassium concentration with a resulting fall in the ratio of sodium to potassium.[20]

The influence of the adrenal cortex on gastric secretion has received considerable study. Tuerkischer and Wertheimer[298] first demonstrated in rats that adrenalectomy produced an increase in the pH and mucin content of fasting gastric juice and a reduction in the volume, acidity, pepsin and renin content of the secretion stimulated by cholinergic drugs. These changes could all be reversed by the administration of adrenocortical extracts. Numerous studies by Gray and his associates[299-301] established the clinical importance of the effects of adrenal steroids on gastric function. Cortisone has been shown, both in normal persons and in patients with Addison's disease, to cause an increase in the basal and nocturnal hydrochloric acid secretion associated with a pronounced rise in the pepsin content of gastric juice. This elevation in peptic activity was reflected in a greatly increased urinary excretion of uropepsin, the output of which was frequently raised to the high levels encountered in patients with peptic ulceration. No effect on urinary uropepsin occurred in patients with pernicious anemia (atrophic gastritis) or in patients previously subjected to total gastrectomy. Experimental observations demonstrated that the action of oxygenated corticosteroids in augmenting the volume and acidity of gastric juice occurs in dogs with denervated as well as innervated gastric pouches.[302] In man the administration of cortisone to patients who have undergone vagotomy has been found to produce an increase in uropepsin excretion.[303] It thus appears that the action of cortisone on the cells of the gastric mucosa may be a direct one and not mediated through nervous pathways. It has not been possible, however, to demonstrate such an effect in vitro.[304]

The development of gastric or duodenal ulcers or the aggravation of persisting ulcers in patients under treatment with cortisone or ACTH has been reported by Gray et al.,[301] Kirsner, Klotz and

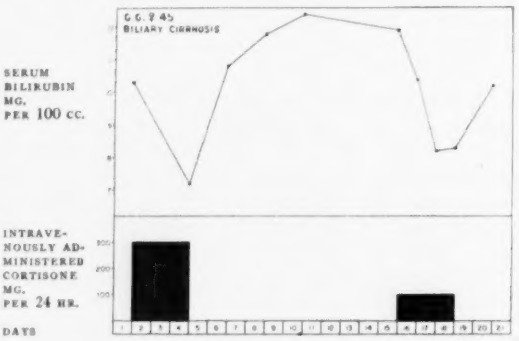

FIGURE 18. *Effect of Cortisone on Serum Bilirubin.*

Palmer[305] and others. It has been suggested from these results that psychogenic and other "stress" factors, long considered of etiologic importance in patients with peptic ulcer, may bring about their adverse effects through the influence of an elevated level of circulating adrenal steroids on gastric secretion. Observations in this laboratory have confirmed the high degree of sensitivity of a rise in urinary uropepsin excretion as an index of adrenocortical stimulation. In fact, a high correlation exists between the urinary content of uropepsin and 17-hydroxycorticoids after adrenocortical activation.

A consistent, though slight, fall in serum bilirubin levels has been repeatedly observed with the administration of ACTH and cortisone to patients with chronic liver disease.[306, 307] An example of such an effect in a patient with biliary cirrhosis who received cortisone intravenously is shown in Figure 18. Flink and Williams[308] have described a decrease in serum bile acid levels after the administration of ACTH to patients with biliary cirrhosis. Although these effects have been ascribed to an anti-inflammatory action of the oxygenated corticosteroids, recent studies in this laboratory[309] have indicated that increased biliary excretion may play a role. Bile was obtained by duodenal intubation before and after cortisone administration to a series of

normal persons and to patients with hepatic and pancreatic disorders. After the intravenous injection of 50 to 100 mg. of cortisone acetate, an increase in the rate of bile flow and in the concentration of bilirubin in the duodenal fluid was consistently observed.

No studies of the influence of cortisone on intestinal absorption in normal subjects or patients with Addison's disease have been reported. The promotion by this hormone of fat, protein and vitamin A absorption in patients with nontropical sprue, however, has repeatedly been observed.[310] The mechanism of this effect is unknown.

Effects on nervous system. In 1944 Heinbecker[311] reported 4 cases of Cushing's syndrome in which degenerative changes in the cells of the paraventricular nuclei could be demonstrated. It was suggested that these changes could be indicative of a hypothalamic disorder responsible for the well recognized abnormality of pituitary-adrenal function in this disorder. The subsequent report of Castor et al.,[312] however, indicated that these lesions were, in all probability, the result of hyperadrenocortical activity rather than the cause of the disease. These workers observed that in cortisone-treated rats chromatolysis and cytoplasmic vacuolation developed in the hypothalamic paraventricular and supraoptic nuclei, as well as in many nuclei of the thalamus.

The electroencephalogram in cases of Addison's disease, which is characteristically slow and not materially benefited by salt or desoxycorticosterone therapy, reverts to normal in a high percentage of patients receiving maintenance doses, 25 mg. a day, of cortisone acetate.[313] Abnormal electroencephalograms have frequently been encountered in patients with Cushing's syndrome[314] or after the administration of cortisone or ACTH.[315, 316] These changes do not appear to be related to alterations in carbohydrate metabolism. Lidz and his coworkers[316] found no correlation between alterations in the electroencephalogram and changes in mood and behavior observed in patients who demonstrated mental disturbances while receiving cortisone. Convulsive seizures have been reported with sufficient frequency during intensive cortisone therapy to indicate a significant effect of adrenocortical hormones on brain excitability.[317] It appears, however, that in the most cases the precipitation of convulsions by cortisone has occurred during the treatment of diseases known to involve the central nervous system. These observations are of interest in view of Woodbury's[146] demonstration that cortisone is capable of increasing the excitability of the brain, as indicated by a lowering of the electroshock seizure threshold.

It has been suggested that the beneficial effects of cortisone and ACTH on diseases such as rheumatoid arthritis are in part due to an analgesic action of these hormones. Grokoest et al.[318] evaluated cutaneous, dental and visceral pain in patients with rheumatoid arthritis before and during the administration of ACTH and cortisone. Cutaneous pain was tested by intradermal injections of saline solution and distilled water, tooth sensitivity by electric stimulation, and visceral pain by distention of a balloon placed in the duodenum. The pain threshold and intensity were similar before and during the administration of the hormones, and no true analgesia could be detected.

Mental symptoms may be prominent in patients with untreated Addison's disease or may be so mild as to escape casual observation. Inability to concentrate and periods of drowsiness may alternate with restlessness and insomnia. As the disease progresses patients become increasingly irritable and apprehensive. Although these symptoms may diminish with desoxycorticosterone therapy, still greater improvement in the patient's mental state occurs when cortisone is given along with desoxycorticosterone.

The patient with Cushing's syndrome may likewise show mental disturbances. In a recent review Plotz, Knowlton and Ragan[314] report that mental symptoms ranging in severity from irritability and depression to major psychoses occurred in one third to two thirds of patients with Cushing's syndrome. The mental illnesses included hysteria, suicidal depression states, simple schizophrenia and paranoia. Of particular interest to the clinician are the psychologic changes that may occur in patients receiving cortisone therapy.[319] Paresthesias in the frontal portions of the head, usually described as a sense of heaviness, fullness or fuzziness, are commonly noted. There is often an increase in appetite. Both loss and increase of libido may be seen. Euphoria, which is an early and frequent symptom, is not necessarily related to the relief of pain or disability, since it may be seen in the normal subject given cortisone. Brody[320] has reported a series of patients in whom the euphoria was soon replaced by psychotic reactions such as delusions, depressions, hostility and ambivalence, which could be correlated with former behavior patterns and seemed to be exacerbations of them. He considered that the rapid action of cortisone in alleviating physical symptoms was experienced by these patients as a threat to the neurotic equilibrium.

In other patients receiving cortisone therapy thinking and behavior may be accelerated to the point of mental excitement, restlessness, wakefulness and a rapidly fluctuating mood. A detailed description of the more severe mental disturbances that may complicate cortisone treatment has recently been given by Clark, Bauer and Cobb.[321] They observed most of the symptoms that may be found in both schizophrenia and affective psychosis. These symptoms, however, appeared in a variable, unpredictable sequence without the consistency of pattern seen in typical cases of psychosis

of spontaneous occurrence. No characteristics of premorbid personality were found that made it possible to anticipate the occurrence or predict the severity or duration of the psychiatric complications. The incidence of the more severe mental disturbances was not clearly related to the dose of cortisone, the duration of the treatment or the magnitude of the metabolic effect. Complete recovery occurred spontaneously in all cases although severe psychoses lasted for as long as two months after cessation of therapy. Similar findings were obtained by Lidz et al.[316] These workers were impressed with the observation that neither ACTH nor cortisone produced transient degradation of mental function such as is seen with drugs capable of inducing toxic psychoses.

Since 1949 psychiatric observations have been made by Fox, Gifford, Bojar and others on a variety of patients treated with cortisone and ACTH at the Peter Bent Brigham Hospital and the Robert Breck Brigham Hospital. In an unpublished paper[322] they have attempted to interpret their findings in the light of certain psychoanalytic concepts as follows:

> The average patient who received therapeutic doses of cortisone or ACTH tended to experience one or more of the following subjective sensations fairly regularly: some feeling of increased well-being, a heightened alertness and keenness of perception, an increase in appetite, a sense of increased energy for physical or intellectual activities, a renewed interest in surroundings and former relations and a greater capacity for emotional contact with others. This average reaction seemed to represent a change in the distribution of instinctual energy, and increase in available energy accompanied by an increased demand for the satisfaction of physiologic and emotional needs.
>
> When the administration of hormone was discontinued, the average patient tended to experience a sense of emptiness and depression, a loss of appetite, a feeling of diminished physical and intellectual energy, and a withdrawal of interest from his environment and emotional contact with others. This phase seemed to represent a depletion of available instinctual energy and a reduction in the total biologic needs of the organism, perhaps analogous to the reduced physiologic intake of the untreated patient with Addison's disease or the hibernating animal.
>
> This sequence of changes in the distribution of instinctual energy tended to parallel changes in the disorder for which the patient was receiving treatment. Energy seemed to increase with symptomatic improvement and to diminish with the reappearance of symptoms when treatment was discontinued. The same changes were observed, however, in patients whose symptoms were unaltered by treatment with cortisone or ACTH, and certain patients who showed marked symptomatic improvement failed to experience any subjective changes whatever.
>
> No consistent differences were observed in the types of psychologic response to cortisone or ACTH. There were variations in the time of onset and duration of response that seemed more specifically related to the dosage and mode of administration.
>
> Every variety of clinical response to the hormones seemed to represent a summation of three principal components, each playing a part in every reaction but its relative importance being determined by the personality structure of the individual patient: the specific physiologic effect of the steroid hormone on the distribution of biologic energy, independent of its effect on symptoms; the instinctual energy that had been fixed in a bodily symptom seemed to be released and made available to the organism when the symptom was modified by the action of the hormone (the same energy seemed to be reinvested in the symptom and withdrawn from the organism when the symptom reappeared); and the response to unconscious phantasies about the nature and action of the steroid hormone, phantasies sometimes as powerful as the hormone's specific physiologic effect.
>
> Patients frequently gave the impression of utilizing their customary psychologic defenses more actively and efficiently during the administration of cortisone. This probably occurred in response to the internal pressure of increased instinctual drives requiring an increase in the effectiveness of the patient's customary mechanisms of emotional control and instinctual integration. Apparently, the steroid hormones had no direct effect on the character or structure of the psychologic defenses themselves.
>
> Certain patients experienced a sense of well-being in an exaggerated form, as if the increased instinctual energy was difficult to regulate within the limits of their customary defenses. Some of these patients described their experiences as intensely pleasurable, in terms of great alertness, physical strength or intellectual prowess, and their behavior suggested a state of euphoria or elation, sometimes approaching a mild hypomania. Apparently they possessed an emotional readiness, and a pre-existing personality structure, that enabled them to experience the physiologic changes induced by ACTH and cortisone as pleasurable subjective sensations, and to feel the increase in instinctual energy as an access of strength — as the action of a powerful life-giving substance.
>
> Other patients experienced similar subjective sensations in an exaggerated form, but they described the same general effects in disturbing and disagreeable terms. They became anxious, rest-

less and wakeful, and they complained of irritability, distractibility and "racing thoughts." Apparently, they perceived the physiologic effects and the increased instinctual drives as threatening to their internal security. Sometimes, these responses seemed to represent a general sense of alarm, as if the patient had become aware of a nonspecific danger to his existing emotional equilibrium, or they were reactions to a specific unconscious fear when certain instinctual conflicts were intensified.

Certain groups of patients who did not react in the usual way to the administration of ACTH and cortisone were studied. Two normal control subjects denied any subjective sensations whatever in response to large doses of the hormones, and it could be shown that both young men were attracted to the experimental situation by an unusually intense need to prove their physical and emotional invulnerability, one by means of his belief in the supremacy of the body and physical activity, and the other by his faith in the omnipotence of logic and conscious control over feelings. A few patients with neurotic symptoms of fatigue and unconscious fears of locomotion responded to ACTH and cortisone with great anxiety and increased inhibitions against movement. Two patients with anorexia nervosa experienced precisely the opposite of the expected "average reaction," refusing to eat altogether, vomiting and complaining of abdominal pains, and withdrawing into a state of mutism and complete immobility. These changes occurred despite a satisfactory rise in urinary uropepsin content. These "negativistic responses" seemed to occur when the intensification of specific instinctual conflicts about eating and locomotion created intolerable anxiety and required an equivalent intensification in the neurotic inhibitions against eating and walking.

When the therapeutic effects of cortisone brought about a sudden improvement in a long-standing pathologic process, some patients had unexpected complications. In some cases there was a recurrence or exacerbation of symptoms in spite of continued treatment with steroid hormones. In others new symptoms were elaborated, replacing previous ones; these included transient conversion symptoms in patients who had a pre-existing hysterical character structure. In other cases previously existing tendencies to psychosomatic disturbance were activated — for instance, the activation of a peptic ulcer that may have been quiescent for many years. It is apparent that the occurrence of certain complications, such as peptic ulcer and hypertension, may be directly conditioned by the physiologic consequences of hormone administration. A comparatively small number of patients experienced more serious psychologic difficulties, varying in extent from mild states of depersonalization to severe psychotic episodes, all of which were self-limited and relatively brief. In all these cases the administration of ACTH and cortisone had apparently led to an intensification of instinctual conflicts that the patient's customary defenses were inadequate to control. In attempts to predict this type of response the number and severity of neurotic traits seemed less important than the degree to which the long-standing pathologic process had acquired an essential importance in maintaining emotional security.

(To be continued)

References

190. Fraser, C. G., Preuss, F. S., and Bigford, W. D. Adrenal atrophy and irreversible shock associated with cortisone therapy. *J. A. M. A.* **149**:1542, 1952.
191. Stebbins, R. B. Cytochemical changes in adrenal cortex of rat following administration of cortisone. *Federation Proc.* **9**:345, 1950.
192. O'Donnell, W. M., Fajans, F. S., and Weinbaum, J. G. Human adrenal cortex after administration of ACTH and cortisone: morphological changes. *Arch. Int. Med.* **88**:28-35, 1951.
193. Sayers, G., and Sayers, M. A. Pituitary-adrenal system. *Recent Progr. in Hormone Research* **2**:81-115, 1948.
194. Sayers, G. Adrenal cortex and homeostasis. *Physiol. Rev.* **30**:241-320, 1950.
195. *Idem.* Personal communication.
196. Fredrickson, D. S., Forsham, P. H., and Thorn, G. W. Effect of massive cortisone therapy on measurements of thyroid function. *J. Clin. Endocrinol. & Metab.* **12**:541-553, 1952.
197. Halmi, N. S., and Barker, S. B. Histo-physiological effects of cortisone on rat pituitary and thyroid. *Endocrinology* **51**:127-134, 1952.
198. Sohval, A. R., and Soffer, L. J. Influence of cortisone and adrenocorticotropin on urinary gonadotrophin excretion. *J. Clin. Endocrinol.* **11**:677-687, 1951.
199. Johnsson, S., and Hogberg, B. Observations on connexion between intermedin and adrenocorticotrophic hormone. *Nature, London* **169**:286, 1952.
200. Hall, T. C., McCracken, B. H., and Thorn, G. W. Skin pigmentation in relation to adrenal cortical function. *J. Clin. Endocrinol. & Metab.* (in press).
201. Wolfson, W. Q., et al. Corticogenic hypothyroidism: its regular occurrence and clinical significance during prolonged therapeutic administration of ACTH or cortisone. *J. Lab. & Clin. Med.* **36**: 1005, 1950.
202. Hill, S. R., Jr., Reiss, R. S., Forsham, P. H., and Thorn, G. W. Effect of adrenocorticotrophin and cortisone on thyroid function: thyroid adrenocortical interrelationships. *J. Clin. Endocrinol.* **10**:1375-1400, 1950.
203. Hardy, J. D., Riegel, C., and Erisman, E. P. Experience with protein bound iodine (PBI): effect of ACTH and cortisone on thyroid function. *Am. J. M. Sc.* **220**:290-292, 1950.
204. Woodbury, D. M., Ghosh, B. N., and Sayers, G. Modification of TSH action by ACTH and cortisone in hypophysectomized rats. *J. Clin. Endocrinol.* **11**:761, 1951.
205. Perry, W. F. Action of cortisone and ACTH on thyroid function. *Endocrinology* **49**:284-288, 1951.
206. Albert, A., Tenney, A., and Ford, E. Effect of cortisone and corticotropin on biologic decay of thyroidal radioiodine. *Endocrinology* **50**:324-326, 1952.
207. Lerman, J., Harington, C. R., and Means, J. H. Physiologic activity of some analogues of thyroxine. *J. Clin. Endocrinol. & Metab.* **12**: 1306-1314, 1952.
208. Beierwaltes, W. H., Wolfson, W. Q., Jones, J. R., Knorpp, C. T., and Siemienski, J. S. Increase in basal oxygen consumption produced by cortisone in patients with untreated myxedema. *J. Lab. & Clin. Med.* **36**:799, 1950.
209. Winter, C. A., Silber, R. H., and Stoerk, H. C. Production of reversible hyperadrenocortinism in rats by prolonged administration of cortisone. *Endocrinology* **47**:60-72, 1950.
210. Brown, R. W., Woodbury, D. M., and Sayers, G. Inhibition of thyrotropin, gonadotropins and prolactin by ACTH. *J. Clin. Endocrinol. & Metab.* **12**:939, 1952.
211. Bookman, J. J., Drachman, S. R., Schaefer, L. E., and Adlersberg, D. Studies on steroid diabetes in man. *J. Clin. Endocrinol. & Metab.* **12**:945, 1952.
212. Plotz, C. M., et al. Effect of hyperadrenal state on connective tissue. *Am. J. Path.* **26**:709, 1950.
213. Baker, B. L. Comparison of histological changes induced by experimental hyperadrenocorticalism and inanition. *Recent Progr. in Hormone Research* **7**:331-373, 1951.
214. Johnson, D. D. Alloxan administration in guinea pig: study of regenerative phase in islands of Langerhans. *Endocrinology* **47**: 393-398, 1950.
215. Becker, B. Diabetic retinopathy. *Ann. Int. Med.* **37**:273-289, 1952.

216. Dana, G., Eversole, S., and Zubrod, C. Clinical entity of retinal aneurysms, glomerular nodules and hyperglycemia. *Bull. Johns Hopkins Hosp.* **90**:323-326, 1952.

217. Baker, B. L., and Whitaker, W. L. Growth inhibition in skin following direct application of adrenal cortical preparations. *Anat. Rec.* **102**:333-347, 1948.

218. Sauer, G. C., et al. Effects of ACTH on certain diseases and physiologic functions of skin. In *Proceedings of the Second Clinical ACTH Conference*. Edited by J. R. Mote. Vol. 2. 716 pp. Philadelphia: Blakiston, 1952. Pp. 529-547.

219. Brunsting, L. A., Slocumb, C. H., and Didcoct, J. W. Effects of cortisone on acute disseminated lupus erythematosus. *Arch. Dermat. & Syph.* **63**:29-48, 1951.

220. Everse, J. W. R., and De Fremery, P. On method of measuring fatigue in rats and its application for testing suprarenal cortical hormone (Cortin). *Acta brev. Neerland.* **2**:152, 1932.

221. Ingle, D. J., and Kuizenga, M. H. Relative potency of some adrenal cortical steroids in muscle-work test. *Endocrinology* **36**:218-226, 1945.

222. Ingle, D. J., Nezamis, J. E., and Morley, E. H. Comparative value of cortisone, 17-hydroxycorticosterone and adrenal cortex extract by continuous intravenous injection in sustaining ability of adrenalectomized rat to work. *Endocrinology* **50**:1-4, 1952.

223. Zierler, K. L., Folk, B. P., Magladery, J. W., and Lilienthal, J. L., Jr. On creatinuria in man. Roles of renal tubule and of muscle mass. *Bull. Johns Hopkins Hosp.* **85**:370-395, 1949.

224. Shy, G. M., Brendler, S., Rabinovitch, R., and McEachern, D. Effects of cortisone in certain neuromuscular disorders. *J. A. M. A.* **144**:1353-1358, 1950.

225. Torda, C., and Wolff, H. G. Effects of adrenocorticotrophic hormone on neuromuscular function in patients with myasthenia gravis. *J. Clin. Investigation* **28**:1228-1235, 1949.

226. Becks, H., Simpson, M. E., Marx, W., Li, C. H., and Evans, H. M. Effects of adrenocorticotropic hormone (ACTH) on osseous system in normal rats. *Endocrinology* **34**:305-310, 1944.

227. Baker, B. L. Modification of body structure by adrenocortical secretions with special reference to regulation of growth. In *Pituitary-Adrenal Function*. 211 pp. Washington, D. C.: American Association for the Advancement of Science, 1950. Pp. 88-95.

228. Demartini, F., Grokoest, A. W., and Ragan, C. Pathological fractures in patients with rheumatoid arthritis treated with cortisone. *J. A. M. A.* **149**:750-752, 1952.

229. Teicher, R., and Nelson, C. T. Osteoporosis and pathological fractures following treatment with ACTH and cortisone. *J. Invest. Dermat.* **19**:205-210, 1952.

230. Reed, C. I., Joseph, N. R., Steck, I. E., and Montgomery, M. M. Effects of ACTH on synovial membrane potentials in rheumatoid arthritis. *Federation Proc.* **9**:104, 1950.

231. Hollander, J. L., Brown, E. M., Jr., and Jessar, R. A. Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as local antiarthritic agent. *J. A. M. A.* **147**:1629-1635, 1951.

232. Ragan, C. F., et al. Effct of ACTH and cortisone on connective tissue. *Bull. New York Acad. Med.* **26**:251-254, 1950.

233. Sacerdote, D., Lustig, E., and Mancini, R. E. Action de la desoxycorticostérone et de la cortisone sur la genèse des fibrilles dans les cultures de fibroblastes. *Compt. rend. Soc. de biol.* **145**:1724, 1951.

234. Castor, W. C., and Baker, B. L. Local action of adrenocortical steroids on epidermis and connective tissue of skin. *Endocrinology* **47**:234-241, 1950.

235. Baker, B. L., Ingle, D. J., and Li, C. H. Histology of lymphoid organs of rats treated with adrenocorticotropin. *Am. J. Anat.* **88**:313-350, 1951.

236. Gordon, A. S., and Katsh, G. F. Relation of adrenal cortex to structure and phagocytic activity of macrophagic system. *Ann. New York. Acad. Sc.* **52**:1-30, 1949.

237. Spain, D. M., Molomut, N., and Haber, A. Biological studies on cortisone in mice. *Science* **112**:335-337, 1950.

238. Howes, E. L., Plotz, C. M., Blunt, J. W., and Ragan, C. Retardation of wound healing by cortisone. *Surgery* **28**:177-181, 1950.

239. Blunt, J. W., Jr., et al. Effect of cortisone on experimental fractures in rabbit. *Proc. Soc. Exper. Biol. & Med.* **73**:678-681, 1950.

240. Ragan, C., Grokoest, A. W., and Boots, R. H. Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis. *Am. J. Med.* **7**:741-750, 1949.

241. Baker, B. L., and Whitaker, W. L. Interference with wound healing by local action of adrenocortical steroids. *Endocrinology* **46**: 544-551, 1950.

242. Findlay, C. W., Jr., and Howes, E. L. Combined effect of cortisone and partial protein depletion on wound healing. *New Eng. J. Med.* **246**:597-604, 1952.

243. Schavel, R. S., Saltzstein, H. C., and Johnson, A. S. Prevention of adhesions in chest and pericardium by cortisone. In *Postgraduate Medicine and Surgery; Surgical Forum, American College of Surgeons*. 667 pp. Philadelphia: Saunders, 1951. Pp. 531-536.

244. Ducommun, P., and Mach, R. S. L'action de l'ACTH sur les adherences dues à l'injection de talc dans la cavité péritonéale des rats: communication préliminaire. *Semaine d. hôp. de Paris* **26**:3170-3172, 1950.

245. Baxter, H., Johnson, L., Mader, V., and Schiller, C. Cortisone as adjunct in treatment of postoperative stiffness of hand. *Canad. M. A. J.* **63**:540-542, 1950.

246. Selye, H. Prevention by somatotrophin of catabolism which normally occurs during stress. *Endocrinology* **49**:197-199, 1951.

247. Dougherty, T. F., and White, A. Influence of hormones on lymphoid tissue structure and function. Role of pituitary adrenotrophic hormone in regulation of lymphocytes and other cellular elements of blood. *Endocrinology* **35**:1-14, 1944.

248. Hills, A. G., Forsham, P. H., and Finch, C. A. Changes in circulating leucocytes induced by administration of pituitary adrenocorticotrophic hormone (ACTH) in man. *Blood* **3**:755-768, 1948.

249. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.* **8**:15-66, 1948.

250. Thorn, G. W., et al. Clinical studies on activity of orally administered cortisone. *New Eng. J. Med.* **245**:549-555, 1951.

251. Kellgren, J. H., and Janus, O. Eosinopenic response to cortisone and A.C.T.H. in normal subjects. *Brit. M. J.* **2**:1183-1187, 1951.

252. Rosenthal, R. L., Wald, N., Yager, A., and Litwins, J. Effects of cortisone and ACTH therapy on eosinophils of bone marrow and blood. *Proc. Soc. Exper. Biol. & Med.* **75**:740, 1950.

253. Gordon, A. S., Piliero, S. J., and Landau, D. Relation of adrenal to blood formation in rat. *Endocrinology* **49**:497-511, 1951.

254. Lanman, J. T., Bierman, H. R., and Byron, R. L., Jr. Transfusion of leukemic leukocytes in man; hematological and physiologic changes. *Blood* **5**:1099-1113, 1950.

255. Padawer, J., and Gordon, A. S. Hormonal influences upon the distribution and fate of eosinophilic leukocyte. *J. Clin. Endocrinol.* **12**:922, 1952.

256. Muehrcke, R. C., Lewis, J. L., and Kark, R. M. Effects of cortisone and heparin on eosinophils in defibrinated human blood. *Science* **115**:377, 1952.

257. Godlowski, Z. Z. Prevention of hormonal eosinopenia and lymphopenia by inhibition of clotting in blood: preliminary report. *Brit. M. J.* **1**:854, 1951.

258. Yoffey, J. M., Metcalf, W. K., Herdan, G., and Nairn, V. Effect of A.C.T.H. and suprarenal extract on bone marrow. *Brit. M. J.* **1**:660-665, 1951.

259. Feldman, J. D. In vitro reaction of cells to adrenal cortical steroids with special reference to lymphocytes. *Endocrinology* **46**:552-562, 1950.

260. Heilman, D. H. Effect of 11-dehydro-17-hydroxycorticosterone and 11-dehydrocorticosterone on migration of macrophages in tissue culture. *Proc. Staff Meet., Mayo Clin.* **20**:318-320, 1945.

261. Baldridge, G. D., Kligman, A. M., Lipnik, M. J., and Pillsbury, D. W. In vitro effects of cortisone on mesodermal tissue. *Arch. Path.* **51**:593-596, 1951.

262. Finch, S. C., Crockett, C. L., Jr., Ross, J. F., and Bayles, T. B. Hematologic changes with ACTH and cortisone therapy of rheumatoid arthritis. *Blood* **6**:1034-1050, 1951.

263. Quittner, H., Wald, N., Susman, L. N., and Antopol, W. Effect of massive doses of cortisone on peripheral blood and bone marrow of mouse. *Blood* **6**:513-521, 1951.

264. Thorn, G. W., et al. Clinical usefulness of ACTH and cortisone. *New Eng. J. Med.* **242**:783-793, 824-834 and 865-872, 1950.

265. Editorial. ACTH and cortisone in hypersplenic syndromes. *J. A. M. A.* **149**:485, 1952.

266. Bethell, F. H., Miller, S., and Meyers, M. C. Administration of ACTH and cortisone in hypersplenic syndromes. In *Proceedings of the Second Clinical ACTH Conference*. Edited by J. R. Mote. Vol. 2. 716 pp. Philadelphia: Blakiston, 1951. Pp. 173-180.

267. Cosgriff, S. W., Diefenbach, A. F., and Vogt, W., Jr. Hypercoagulability of blood associated with ACTH and cortisone therapy. *Am. J. Med.* **9**:752-756, 1950.

268. Monto, R. W., Brennan, M. J., Margulis, R. R., and Smith, R. W. Observations on effect of ACTH and cortisone in coagulation of blood. *J. Lab. & Clin. Med.* **36**:1008, 1950.

269. Fahey, J. L. Effect of ACTH on whole blood coagulability. *Proc. Soc. Exper. Biol. & Med.* **77**:491-494, 1951.

270. Perera, G. A. Altered metabolic response prior to development of hypertensive vascular disease. *Am. Heart J.* **42**:308-310, 1951.

271. Wolferth, C. C., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A., and Hafkenschiel, J. H. Observation on results of subtotal adrenalectomy in the treatment of severe, otherwise intractable hypertension and their bearing on mechanism by which hypertension is maintained. *Ann. Int. Med.* **35**:8-18, 1951.

272. Goldblatt, H. Studies in experimental hypertension: pathogenesis of experimental hypertension due to renal ischemia. *Ann. Int. Med.* **11**: 69-103, 1937.

273. Turner, L. B., and Grollman, A. Role of adrenal in pathogenesis of experimental renal hypertension as determined by study of bilaterally adrenalectomized nephrectomized dog. *Am. J. Physiol.* **167**:462-471, 1951.

274. Perera, G. A., Knowlton, A. I., Lowell, A., and Loeb, R. F. Effect of desoxycorticosterone acetate on blood pressure of man. *J. A. M. A.* **125**:1030-1035, 1944.

275. Selye, H. General adaptation syndrome and diseases of adaptation. *J. Clin. Endocrinol.* **6**:117-230, 1946.

276. Gaudino, M. Las suprarrenales en la hipertensión arterial nefrogena. *Rev. Soc. argent. de. biol.* **20**:470-486, 1944.

277. Knowlton, A. I., Loeb, E. N., Stoerk, H. C., and Seegal, B. C. Development of hypertension and nephritis in normal and adrenalectomized rats treated with cortisone. *Proc. Soc. Exper. Biol. & Med.* **72**:722-725, 1949.

278. Masson, G. M. C., Corcoran, A. C., Dustan, H., and Page, I. H. Cardiovascular and metabolic effects of cortisone, hydrocortisone and other steroids in rat. *Am. J. M. Sc.* **224**:175-185, 1952.

279. Perera, G. A. Endocrine factors in hypertension. *Bull. New York Acad. Med.* **28**:43-51, 1952.

280. Haynes, F. W., Forsham, P. H., and Hume, D. M. Effect of pituitary adrenocorticotropin, cortisone, desoxycorticosterone and epinephrine on plasma hypertensinogen and renin concentration of dogs. *Am. J. Physiol.* (in press).

281. Perera, G. A. Cortisone and blood pressure. *Proc. Soc. Exper. Biol. & Med.* **76**:583-585, 1951.

282. Perera, G. A., Fleming, T. C., Pines, K. L., and Crymble, M. Cortisone in hypertensive vascular disease. *J. Clin. Investigation* **29**: 739-744, 1950.

283. Dustan, H. P., Corcoran, A. C., Taylor, R. D., and Page, I. H. Cortisone and ACTH in essential hypertension: establishment of renal glycosuria. *Arch. Int. Med.* **87**:627-635, 1951.

284. Friedman, S. M., Friedman, C. L., and Nakashima, M. Action of cortisone of cardiovascular-renal effects of desoxycorticosterone. *Am. J. Physiol.* **163**:319-325, 1950.

285. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J. Further studies on treatment of congenital adrenal hyperplasia with cortisone: control of hypertension with cortisone, with discussion of variations in type of congenital adrenal hyperplasia and report of case with probable defect of carbohydrate-regulating hormones. *J. Clin. Endocrinol. & Metab.* **12**:1015-1030, 1952.

286. Robson, H. N., and Duthie, J. J. R. Capillary resistance and adrenocortical activity. *Brit. M. J.* **2**:971-977, 1950.

287. Ramey, E. R., Goldstein, M. S., and Levine, R. Action of nor-epinephrine and adrenal cortical steroids on blood pressure and work performance of adrenalectomized dogs. *Am. J. Physiol.* **165**: 450-455, 1951.

288. Fritz, I., and Levine, R. Action of adrenal cortical steroids and nor-epinephrine on vascular responses of stress in adrenalectomized rats. *Am. J. Physiol.* **165**:456-465, 1951.

289. Brust, A. A., Ransohoff, W., and Reiser, M. F. Blood pressure responses to ACTH and cortisone in normotensive and hypertensive subjects in resting state and during autonomic blockade with tetraethylammonium chloride. *J. Clin. Investigation* **30**:630, 1951.

290. Myers, J. D., and Taylor, W. J. Effects of cortisone and ACTH on splanchnic circulation and metabolism. *J. Clin. Investigation* **31**:651, 1952.

291. Stamler, J., Pick, R., and Katz, L. R. Intensification of cholesterol-induced atherogenesis by cortisone in chick. *Circulation* **4**:461, 1951.

292. Etheridge, E. M., and Hoch-Ligeti, C. Lipid deposition in aortas in younger age groups following cortisone and adrenocorticotrophic hormone. *Am. J. Path.* **28**:315-319, 1952.

293. Bloom, B., and Pierce, F. T., Jr. Relationship of ACTH and cortisone to serum lipoproteins and atherosclerosis in humans. *Metabolism* **1**:155-162, 1952.

294. Pierce, F. T., Jr., and Bloom, B. Relationship of ACTH and cortisone to serum lipoproteins of rabbit. *Metabolism* **1**:163-171, 1952.

295. Horwitz, O., Sayen, A., Naide, M., and Hollander, J. L. Measurements of certain cardiovascular responses to ACTH and cortisone in man. *Am. J. M. Sc.* **221**:669-671, 1951.

296. Somerville, W., Levine, H. D., and Thorn, G. W. Electrocardiogram in Addison's disease. *Medicine* **30**:43-79, 1951.

297. Arons, W. L., and Lown, B. Unpublished data.

298. Tuerkischer, E., and Wertheimer, E. Adrenalectomy and gastric secretion. *J. Endocrinology* **4**:143-151, 1945.

299. Spiro, H. M., Reifenstein, R. W., and Gray, S. J. Effect of adrenocorticotropic hormone upon uropepsin excretion. *J. Lab. & Clin. Med.* **35**:899-910, 1950.

300. Gray, S. J., Benson, J. A., Reifenstein, R. W., and Spiro, H. M. Chronic stress and peptic ulcer. I. Effect of corticotrophin (ACTH) and cortisone on gastric secretion. *J. A. M. A.* **147**:1529-1537, 1951.

301. Gray, S. J., Benson, J. A., Jr., Spiro, H. M., and Reifenstein, R. W. Effects of ACTH and cortisone upon stomach. *Gastroenterology* **19**:658-673, 1951.

302. Zubiran, J. M., Kark, A. E., and Dragstedt, L. R. Effect of ACTH on gastric secretion in experimental animals. *Gastroenterology* **21**:276-279, 1952.

303. Gray, S. J. Personal communication.

304. Davenport, H. W., and Chavré , V. J. Lack of effect of adrenal hormones upon gastric acid secretion. *Endocrinology* **47**:193-197, 1950.

305. Kirsner, J. B., Klotz, A. P., and Palmer, W. L. Unfavorable course of gastric ulcer during administration of ACTH and cortisone. *Gastroenterology* **20**:27-29, 1952.

306. Bluemle, L. W., Jr., Sborov, E. M., Stokes, J., Jr., Gyorgy, P., and Neefe, J. R. Use of adrenocorticotrophic hormone in chronic liver disease (three cases). In *Proceedings of the First Clinical ACTH Conference*. 607 pp. Edited by J. R. Mote. Philadelphia: Blakiston, 1950. Pp. 505-508.

307. Havens, W. P., Jr., Myerson, R. M., and Carroll, I. N. Effect of ACTH, cortisone and progesterone on patients with chronic hepatic disease. *Metabolism* **1**:172-178, 1952.

308. Flink, E. B., and Williams, C. H. Effect of corticotropin administration on blood bile acids and pruritus in biliary cirrhosis. *J. Clin. Investigation* **31**:627, 1952.

309. Patterson, P., Dingman, J. F., and Thorn, G. W. Unpublished data.

310. Adlersberg, D., Colcher, H., and Drachman, S. R. Studies on effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) in sprue syndrome. *Gastroenterology* **19**:674-697, 1951.

311. Heinbecker, P. Pathogenesis of Cushing's syndrome. *Medicine* **23**: 225-247, 1944.

312. Castor, C. W., Baker, B. L., Ingle, D. J., and Li, C. H. Effect of treatment with ACTH or cortisone on anatomy of brain. *Proc. Soc. Exper. Biol. & Med.* **76**:353-357, 1951.

313. Lewis, R. A., Hoffman, W. C., and Thorn, G. W. Electroencephalogram in Addison's disease. *Bull. Johns Hopkins Hosp.* **70**:335-361, 1942.

314. Plotz, C. M., Knowlton, A. I., and Ragan, C. Natural history of Cushing's syndrome. *Am. J. Med.* **13**:597-614, 1952.

315. Hoefer, P. F. A., and Glaser, G. H. Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy. *J. A. M. A.* **143**:620-625, 1950.

316. Lidz, T., Carter, J. D., Lewis, B. I., and Surratt, C. Effects of ACTH and cortisone on mood and mentation. *Psychosom. Med.* **14**: 363-377, 1952.

317. Baehr, G., and Soffer, L. J. Treatment of disseminated lupus erythematosus with cortisone and adrenocorticotropin. *Bull. New York Acad. Med.* **26**:229-234, 1950.

318. Grokoest, A. W., Vaillancourt, deG., Gottsagan, R., and Ragan, R. Lack of analgesic effect of cortisone and ACTH. *J. Clin. Investigation* **30**:644, 1951.

319. Palmer, W. L. Psyche, soma and steroids. *Am. J. Med.* **10**:275-277, 1951.

320. Brody, S. Psychiatric observations in patients treated with cortisone and ACTH. *Psychosom. Med.* **14**:94-103, 1952.

321. Clark, L. D., Bauer, W., and Cobb, S. Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. *New Eng. J. Med.* **246**:205-216, 1952.

322. Fox, H. M., et al. Unpublished data.

MEDICAL INTELLIGENCE

PRESENTATION OF THE FETUS THROUGH THE RECTUM*

Report of a Case of Unusual Rupture of the Uterus

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THE diagnostic term "rupture of the uterus" is used to denote perforation from any cause after fetal viability has been established.[1] Although this obstetric accident may occur in 1 of 3000 deliveries[2] and account for 5 per cent of the maternal deaths[1] in the United States, the incidence is as high as 1 in 100 in certain areas of Africa[3, 4] and China[5] and the Middle East. In addition, these ruptures may be associated with a commensurate and substantial mortality.

Among the patients at term admitted to the "Hareem" pavilion of the Dhahran Health Center, a 200-bed general hospital maintained by the Arabian American Oil Company in Saudi Arabia for native employees and their families, the number of perforated uteri approaches 1 in 50.

This incredible incidence among desert women occurs primarily in the multiparas whose successive labors are complicated by dystocia secondary to a fibrosis and eventual stenosis of the posterior vagina. The pathologic state has never been satisfactorily investigated. Allegedly, it is a terminal manifestation of a custom practiced by young native mothers in the immediate post-partum period. These women place rock salt into the vaginal vault in an attempt to restore normal contours more quickly. With repetition of this practice, a progressive stenosing fibrosis of the birth canal develops in an appreciable number. The vast majority of perforations occur in this group of women.

Another factor concerned with obstetrics as well as tolerance to disease in these regions and possibly of equal importance in its relation to uterine rupture is the poor nutritional state of the mothers.[4] The average diet in the Middle East and particularly in Saudi Arabia is high in carbohydrate and generally low in protein, fat and vitamins. There is some experimental evidence that poor nutrition predisposes to uterine perforation.[3]

Frequently, especially when delivery might appear to be unduly delayed, these women have been known to receive vigorous assistance in their labor from members of their families or midwives. This provides a more dynamic factor to abet perforation.

The following case, in addition to illustrating a perforation of the uterus at term in a native woman with vaginal stenosis, presents the dramatic complication of the eventual retroperitoneal descent of the vertex followed by perforation of the anterior wall of the rectum and presentation through a dilated anus.

CASE REPORT

S. B. A. (D.H.C. 51-1935), a 30-year-old Arabian woman (gravida 5, para 4), was admitted to the hospital at term on September 13, 1951, 24 hours after the onset of labor. Though prolonged, labor had apparently been uncomplicated until just prior to admission. The patient had been assisted by a midwife, who, allegedly, had merely maintained pressure on the perineum. Manual abdominal assistance was steadfastly denied. One hour prior to admission, it was noted that the head of the fetus was presenting at a dilated anus. The pains increased in severity as the patient became weak and faint. Bloody discharge had not occurred from either the vagina or the rectum. From the history, the membranes were apparently intact. The patient was taken to the Dhahran Health Center by her family. The past history was noncontributory except for the indication that vaginal tamponade with salt had been used after previous deliveries.

Physical examination showed a patient of small stature who was well nourished and apparently of the stated age, but in acute distress. Respirations were short and grunting, and she was "bearing down" with considerable voluntary effort. There was moderate sweating, but the color was good. Positive findings were mainly limited to the abdomen and perineum. The usual contour of the gravid uterus was absent. Uterine contractions had ceased. There was moderate tenderness and spasm over the lower quadrants and over indefinite masses. In the right upper quadrant the edge of a firm, slightly mobile mass was palpable. It measured approximately 20 cm. in diameter. In the suprapubic region and extending into the right side, some fetal parts were felt. No fetal heart sounds were heard. The vertex was presenting through a dilating (6-cm.) anus in a characteristic left occiput anterior position. The presenting part was molded considerably. No membranes were visualized. The fetal scalp was cyanotic and slightly macerated. The anal ring was swollen, lobulated and edematous, presenting an appearance not unlike that of giant thrombosed hemorrhoids. Vaginal examination was limited. The posterior vaginal wall and the perineal body were markedly attenuated and awkwardly displaced anteriorly. The vaginal canal was practically obliterated. Neither the cervix nor the full extent of the vagina could be demonstrated. There was no blood in the vagina or other indication of cervicovaginal tear.

The temperature was 100°F. (37.8°C.), the pulse 140, and the respirations 26. The blood pressure was 110/70.

X-ray films taken before the arrival of the surgeon were difficult to interpret. The fetal parts appeared to lack tone and from their position were consistent with the impression of intrauterine death. The preoperative diagnosis was: rupture of a gravid uterus and rectum, with a nonviable fetus.

Supportive measures, including intravenous injection of fluids, were instituted immediately; 300,000 units of crystalline penicillin and 200 mg. of aureomycin were given intramuscularly and intravenously with fluids respectively. A Levine tube was placed in the stomach, and Wangensteen suction instituted. The patient's blood was typed and crossmatched, and 1000 cc. of Type B, Rh positive blood was made available. One and a half hours after admission she was taken to the operating room.

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Through a 22-cm. suprapubic midline incision, the peritoneum was opened. There was no intraperitoneal soiling by blood or intrauterine contents. The lower circumferential segment of the uterus was completely infarcted, thin, friable and necrotic, but the serosa was intact. Although the infarction extended into the left adnexa, the uterine perforation was more confined to the posterior inferior segment. The presenting part had advanced anterior to the cul-de-sac. This was subsequently confirmed. The markedly tonic but viable upper uterine segment was displaced into the right upper quadrant.

A transverse incision was made through the black, gangrenous uterine wall 4 cm. from the bladder reflection. Bloody amniotic fluid, estimated at 200 to 300 cc., was aspirated. The fetus was found with the vertex in essentially left occiput anterior position with the back toward the operator. With gentle traction from above and perineal taxis from below, the head was disengaged, and a dead, male fetus, fully developed but slightly macerated, was delivered. No attempt at resuscitation was made. The placenta had separated completely and lay posteriorly in the lower segment.

Before further exploration a subtotal hysterectomy and left salpingo-oophorectomy was carried out. Only the right uterine artery was identified, ligated and transfixed with No. 1 silk sutures. During this procedure an attempt was made to find the cervix, which, however, was never at any time positively identified. Combined intra-abdominal and digital exploration with probing by an assistant from below with a rubber catheter did not reveal continuity of the vagina with the peritoneal cavity. This was not considered proof of cervicovaginal continuity but only as an indication that the vagina was not directly involved in the rupture.

The extent of the rectal perforation was determined by location of the upper or visible edge and the placing of multiple traction sutures of No. 00 silk through all identifiable layers of its circumference. An encouraging finding was the collapsed and empty state of the entire proximal portion of the colon. The rent measured, roughly, 8 by 6 cm. and was closed transversely with 2 layers of mattress sutures of No. 00 silk. A No. 24 F. rubber catheter was then introduced through the rectum and advanced above this closure.

With an assistant's hand in the vagina, an incision was made through what was considered the region nearest the posterior fornix. A No. 18 F. catheter and 2 cigaret drains were then placed through this rent into the pelvis, anterior and above the rectal closure. A partial reperitonealization was carried out with No. 00 chromic catgut. Three suprapubic Penrose drains were placed in the pelvis and brought out through the lower extent of the abdominal wound. The peritoneum was closed with a continuous No. 0 chromic catgut suture. No. 28 stainless-steel wire was used in stay sutures placed through all layers, with the exception of the skin and subcutaneous tissue, and interrupted sutures of No. 34 stainless-steel wire were used to approximate the anterior-rectus-muscle sheath.

A loop transverse colostomy was then produced in the right upper quadrant, the bowel being sewn to all layers and placed over a glass rod. All drains were sutured to the adjacent skin edges. During the procedure the patient received 1000 cc. of bank blood. The blood pressure at the conclusion was 115/70, with a pulse of 140. A No. 18 F. Foley catheter was left in the bladder.

Postoperatively the patient did remarkably well. The temperature was rarely over 100°F. and was normal in 1 week. Antibiotic therapy consisted of 300,000 units of crystalline penicillin intramuscularly every 6 hours and 200 mg. of aureomycin twice a day, given intravenously until the 3d day, when 100 mg. four times a day was administered by mouth. Parenterally administered fluid consisted of 2000 cc. of 5 per cent and 10 per cent glucose in distilled water supplemented with saline solution in volume for volume replacement of Levine-tube gastric aspirate. The colostomy was opened with a catheter in the proximal loop on the 2d postoperative day, and completely opened 3 days later. Oral feedings began and were progressed from the 2d day. The patient was ambulatory from the 5th day. Drainage from the abdominal wound as well as the vagina was minimal. All suprapubic drains were out by the 7th day, and the vaginal drains were removed on the 14th day. Saline irrigations through a well established vaginal tract were continued for another week and then discontinued. The patient was discharged with a well functioning colostomy, a healed abdominal wound and slight drainage from the vagina on the 27th postoperative day.

The patient was readmitted to the hospital on October 31 (D. H. C. 51-2211), when a small rectovaginal fistula was demonstrated in the posterior vaginal wall at the former drainage site. In addition a rectal stricture was suspected, but exploratory laparotomy by Dr. Harold Lohnaas 1 month later was reported as revealing a patent rectal lumen. Adhesions were lysed. On December 12 an attempt was made to carry out a transvaginal repair, of the small fistula located high in the posterior wall in a mass of cicatricial tissue. No cervical os was identified. The repair broke down within 2 weeks. The patient was therefore discharged on December 31, to be followed. The colostomy was still functioning well.

On January 20, 1952 (D. H. C. 52-174), the patient was admitted again, and a second attempt was made by Dr. I. K. Mikhail on February 7 to close the fistula. The patient was discharged on February 17, when the fistula had not reopened. The colostomy was to be closed in 2 months if the fistula did not recur.

On March 23 (D. H. C. 52-926) careful examination revealed that the fistula had healed completely. Therefore, the colostomy was closed on March 30. On the 7th postoperative day the patient was discharged with a primary wound closure and a normally functioning bowel.

Discussion

Many *predisposing* factors have been recognized and implicated in rupture of the uterus. These could be summarized as follows: multiparity,[1] previous cesarean section,[2, 6] disproportion[2, 4, 6, 7] abnormal presentation,[2] uterine abnormalities of many types (that is, congenital,[8] postseptic state,[3] placental erosion[2] and tumors,[1]) obstructions in the birth canal[1, 4, 9] and chronic nutritional deficiencies.[3, 4] In addition, more dynamic or precipitating causes have been cited, such as manipulative delivery,[2, 6] use of oxytocic drugs,[2] severe or prolonged labor[2] and trauma.[2]

The cicatricial stenosis of the posterior vagina that was the predisposing factor to uterine perforation in this patient apparently did not prevent conception. From the number of patients with this condition who are able to conceive, it is also apparent that no concomitant obstruction is produced in the endocervical canal by the post-partum custom of introducing salt into the posterior vagina.

The extraordinary uterine perforation reported is considered remarkable in that the anal or rectal position of the presenting part was unassociated with demonstrable cervical, vaginal or sphincter laceration. The descent (Fig. 1) was accomplished entirely retroperitoneally — a feat that incriminates some method of assistance to labor since the

normal expulsive forces must either have ceased or have been sharply diminished after the actual rupture.

The patient survived after prompt hysterectomy, left salpingo-oophorectomy, closure of the rectal perforation and a proximal transverse colostomy. The colostomy was closed seven months later after successful repair of a rectovaginal fistula that, in retrospect, might have been avoided if less drastic methods of pelvic drainage had been utilized.

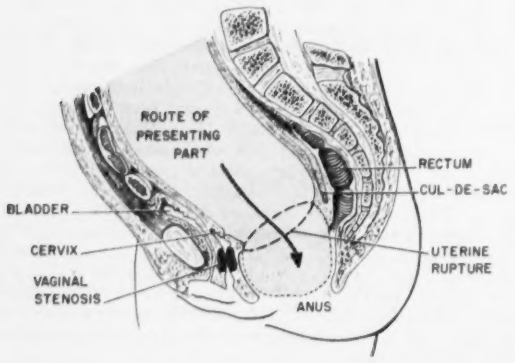


FIGURE 1. *Sagittal Drawing, Illustrating the Mechanism of Retroperitoneal Perforation of the Uterus and Rectum, with the Appearance of the Presenting Vertex at the Anus. This complication was produced by a vaginal stenosis, which resulted from a native custom described in the text.*

REFERENCES

1. Eastman, N. J. *Williams Obstetrics.* Tenth edition. 1176 pp. New York: Appleton-Century, 1950.
2. Fitzgerald, J. E., Webster, A., and Fields, J. E. Ruptured uterus: report of 42 cases. *Surg., Gynec. & Obst.* **88**:652-660, 1949.
3. Gillman, J., Gilbert, C., and Gillman, T. S. Rupture of uterus of nutritional origin: experimental study in albino rat. *S. African J. M. Sc.* **12**:153-160, 1947.
4. Harris, B. P., and Angawa, J. O. W. Rupture of uterus in East Africa: note on its incidence and aetiology in women of Kikuyu tribe. *J. Obst. & Gynaec., Brit. Emp.* **58**:1030-1033, 1951.
5. Whitacre, F. E., and Fang, L. Y. Management of rupture of uterus: report of 44 cases. *Arch. Surg.* **45**:213-234, 1942.
6. Watt, G. L. Rupture of uterus. *Am. J. Obst. & Gynec.* **59**:490-497, 1950.
7. Delfs, E., and Eastman, N. J. Rupture of uterus (analysis of 53 cases). *Canad. M. A. J.* **52**:376-381, 1945.
8. Stander, H. J. *Textbook of Obstetrics.* Ninth edition. 1277 pp. New York: Appleton-Century, 1945.
9. Melody, G. F. Obstructed uterine cervix. *Surg., Gynec. & Obst.* **88**: 50-61, 1949.

AMERICAN TOUR

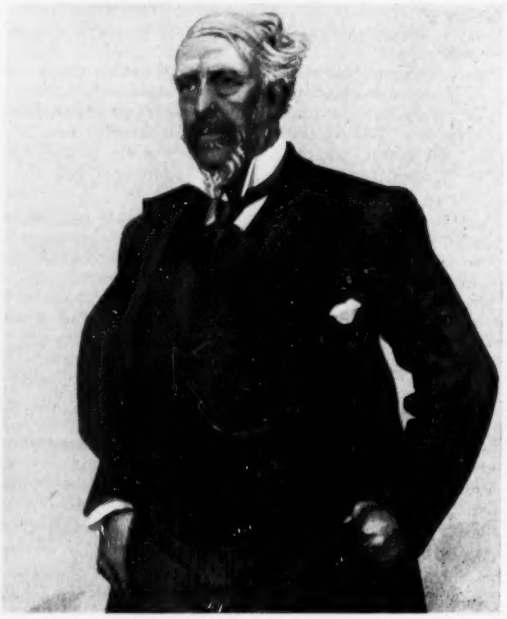
IN September, 1883, Sir William MacCormac, a prominent London surgeon, and Lady MacCormac visited America.

One of the two typewritten accounts of this American Tour is on deposit at St. Thomas's Hospital Library, in London; the other has recently been presented to the Boston Medical Library. The following excerpt is taken from Sir William's account of his visit to Boston.

Boston, Monday, September 10th

Visited the art museum, the annual foreign and home exhibitions, the latter is very interesting, containing only American products, as well in arts, manufactures, and produce of various kinds. Afterwards I went to the Massachusetts General Hospital, the City Hospital, and the new medical school building. Dr. Charles B. Porter very kindly escorted me in his carriage. The Massachusetts Hospital is the oldest in the city, it is built on the edge of the Charles River. The wards are for the most part square, and there are also isolation wards. The wards are ventilated by windows opening at the top, by open fires, and by openings in the ceiling connected with an open roof tree, air at any required temperature, cool in summer and warm in winter, is forced in by an engine. The walls are painted, the floors pitch-pine. The surgeons are,

Dr. Homans,
Dr. Bigelow,
Dr. Hodges,
Dr. Porter,
Dr. Warren,
Dr. Beach.



SIR WILLIAM MACCORMAC

Dr. Beach showed me his wards and cases. Two surgeons are on duty for a spell of four months, and then they have vacation for eight months, each takes charge of about 125 beds. I saw a very interesting case of traumatic aneurismal varix, after gunshot of thigh. The sac extended from the groin nearly to the knee, the operation theatre is very fine, large and well appointed, with a statue of the Apollo Belvedere at the top. It is much larger than the St. Thomas's theatre, and is probably the finest in the United States, or, indeed, anywhere. In the center of the floor is an ingenious chair for operations, contrived by Dr. Bigelow. The patient can be quickly fixed in al-

most any position, and the body can be instantly placed head down and heels up, in case of faintness. Glazed cases for instruments are distributed around the very spacious area, in one of which is placed the original conical sponge with which ether was first administered by Morton, on a patient of Dr. Warren's.

There is a room for administering ether before bringing the patient in, and three "recovery rooms," with several beds in them, in one of which the patient remains until thoroughly recovered from the anaesthetic. Much time is thus saved in the conduct of the operations themselves.

Saturday is the principal operating day, the surgeons operate alternately.

A nursing school is attached, not unlike the Nightingale School. They have a separate building, which seems nicely furnished, in the hospital grounds. The hospital nurses look extremely nice in their high topped Quaker caps.

The p.m. room is very finely equipped. The p.m. table has a large grating in the centre, about eighteen inches square, through which passes a strong down draught, carrying away the effluvia completely, so that, even in hot weather, there is no smell.

The viscera on removal are put into a glass covered recess in the side of the room, like an evaporating chamber in a chemist's laboratory, and there, too, is a strong up draught, when the glazed windows in front are raised. A trough table in it, on which the viscera are laid, is ready for use, and no smell troubles the operators. This arrangement, the invention of Dr. Bigelow, is stated to answer perfectly.

We then visited the new school buildings, very handsome and complete. Very handsome entrance hall, staircase, lecture-halls, and museum. The school, which numbers about 250 students, is in connection with, and under the control of, Harvard University, whose authorities encourage a high order of education and examination amongst the students, many of the medical students possessing degrees in arts.

A recognized holiday vacation occupation with some of the poorer students is to serve as attendants in the hotels of the summer resorts in the White Mountains, and visitors, knowing this, often fee them handsomely. At such an hotel, they received from Mr. Vanderbilt 100 dollars apiece on one occasion. They are exempted from all menial work. An institution in connection with the hospital deserves mention, a central office for obtaining nurses, there a registry and record of suitable persons is kept, and those employed and those who are at the moment disengaged are known, and can at once be made available on the shortest notice. The character of their former service is kept in a book, accessible to those requiring their services. A doctor, for instance, requires a nurse, it may be a hundred miles away in the country, he telegraphs to the office, the secretary telephones to the nurse, and she leaves by next train. Massachusetts Hospital is open to all comers, it is governed by trustees, supported by voluntary contributions, and contains four hundred beds.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39081

PRESENTATION OF CASE

A thirty-nine-year-old woman was admitted to the hospital because of recurrent bouts of itching and jaundice.

Four years prior to admission generalized pruritus developed, lasting four months; it resulted in fatigue and insomnia, but was not accompanied by any other signs or symptoms. One year later pruritus again developed; at that time an enlarged liver and spleen were discovered by her physician, and a Graham test was reported negative. One month after the onset of this, her second bout of itching, generalized icterus ensued, possibly accompanied by light-colored stools and dark urine. This lasted three months, during which the patient lost 14 pounds, which she subsequently regained. At this time also a basal metabolic rate of + 20 per cent was discovered, and she was seen in the Endocrine Clinic of another hospital but no signs of thyrotoxicosis were found. A slight recurrence of symptoms occurred a year later after a New Year's Eve party at which she had had several cocktails. Eighteen months later the patient had an episode of sore throat, fever with a temperature of 102°F., generalized fatigue and pruritus, dark urine and light stools followed in a short time by icterus. The fever disappeared within a few days, but the patient was hospitalized for nineteen days. The entire illness lasted about three months. She was free of symptoms until a week before admission, when she began to have itching, light stools, dark urine and nausea but no vomiting. Anorexia, fatigue and slight jaundice soon developed. She did not notice any fever at the onset of the present episode. Recently, she had had a mild nosebleed; her menstrual flow had not been excessive.

There was no history of exposure to toxins. The patient did not smoke and drank only rarely. She took no medication except Anacin for dysmenorrhea. The past history revealed ankle edema and albuminuria during her only pregnancy.

Physical examination revealed an obese woman in no distress, lying flat in bed. There was slight icterus of the skin and scleras; there were spider angiomas on the right cheek and left anterior part of the chest. The heart and lungs were normal. The liver edge was palpable at the level of the umbilicus, and the spleen 6 cm. below the costal margin. Both were slightly tender.

The temperature was 98°F., the pulse 96, and the respirations 20. The blood pressure was 130 systolic, 84 diastolic.

The urine was cloudy amber, had a specific gravity of 1.015 and gave a + test for albumin and bile and a negative test for sugar; the sediment contained 1 red cell, 3 white cells and a rare granular cast per high-power field. The urinary urobilinogen was 5.1 Ehrlich units. Examination of the blood showed a hemoglobin of 14.4 gm. per 100 cc. and a white-cell count of 12,000, with 58 per cent neutrophils, 35 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 1 mm. in fifteen minutes and 22 mm. in one hour. The reticulocyte count was 0.8 per cent. The alkaline phosphatase was 8.9 units, the bilirubin 2.4 mg. direct and 4.4 mg. total, the total protein 7.16 gm., the albumin 4.84 gm., and the globulin 2.32 gm. per 100 cc., with an albumin-globulin ratio of 2.1. The bromsulfalein test showed 29 per cent retention of the dye; the cephalin flocculation was + in twenty-four and ++ in forty-eight hours, the thymol turbidity 3.0 units per 100 cc., and the thymol flocculation negative. The blood Hinton reaction was negative. The stool was light brown and gave a negative guaiac test. A Graham test faintly demonstrated the gall bladder; no calculi were seen. An upper gastrointestinal series showed no significant abnormality.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Chester M. Jones*: In this case recurrent intrahepatic disease started four years before admission, with itching but without jaundice as the outstanding feature. In most cases in which itching is secondary to biliary-tract disease, there is frank obstruction, usually external to the liver — the commonest type of obstruction being a stone in the common duct. With infectious hepatitis serious itching is frequent; there the obstruction is due to an intrahepatic block. In either event as a rule jaundice is obvious. But in certain cases in either of these two categories itching may be the first symptom and jaundice is a much later development.

Subsequently, in the case under discussion, jaundice did develop in at least three out of five separate attacks. Three years before admission it was proved that the patient had a large liver and spleen so I am perfectly safe in saying that she had intrahepatic disease.

I am at a loss to interpret the basal metabolic rate of + 20 per cent. It probably had no real diagnostic significance, and I am going to disregard it.

The patient had fever with at least one of the attacks of itching and jaundice. It implies but does not prove that there was a biliary-tract infection that subsided when better drainage was established, — in other words cholangitis, to use a general term, — but other diseases that involve the liver are characterized by fever, one of which is infiltrative disease, such as lymphoma of one form or another. Fever also occurs not infrequently with metastatic cancer although I should think that cancer was unlikely here with a four-year history. Fever is a commonplace, rather than a rarity, in the type of disease that we classify as cirrhosis, regardless of the type. Usually it is of short duration unless there is a true intrahepatic biliary-tract infection. There were no chills mentioned with any of these attacks, which may be an important negative finding.

The mild nosebleed was an isolated incident; it may have been due to some change in the coagulation mechanism as a result of intrahepatic disease but more likely was a pure coincidence.

When the patient entered the hospital, she was moderately jaundiced and spider angiomas were noted. I do not think one can overemphasize the diagnostic importance of so-called spider angiomas — they usually mean long-standing liver disease except in the pregnant woman. It is true that spider angiomas have been demonstrated in infectious hepatitis, viral in origin, in the course of an acute attack, but that is unusual; almost always they strongly suggest the presence of progressive, continuing chronic intrahepatic disease. Chronic portal cirrhosis is the most common type, but the angiomas may occur in so-called biliary cirrhosis, which is a less common disease. They do not occur from simple extrahepatic block in my experience, unless the block occurred intermittently over a long enough period — years or months.

About the laboratory data, the albuminuria I think is simply associated with bile in the urine — at least I should not try to attach any particular importance to it. Bile in the urine means an excessively high serum bilirubin with a spill into the urinary tract; it can be due to any type of jaundice if sufficient in degree. There was no complete external block or anything approaching it because the urobilinogen content of the urine was high. It there had been much obstruction to extrahepatic biliary drainage, one would have expected a normal, low or completely absent urobilinogen in the urine; therefore this single laboratory test implies diffuse intrahepatic disease rather than external block of extreme degree.

I suppose the reticulocyte count was included to be sure that there was no suggestion of either acquired or primary hemolytic jaundice. If the patient had a serious type of hemolytic jaundice, I should expect, with the degree of jaundice present, that she would have had a high reticulocyte count.

In favor of block to the flow of bile is the elevation of the alkaline phosphatase to a moderate but not to a high degree. As a rule, a high degree of elevation of alkaline phosphatase, from 15 to 40 Bodansky units or higher, goes with cancer, and the second highest with stone; the intrahepatic type of obstruction is the most likely to have the

*Physician, Massachusetts General Hospital.

relatively low figure rather than the very high figure. It should be remembered, however, that this laboratory test can be misleading. We have seen a good many cases of infectious hepatitis or intrahepatic disease even without jaundice in which the phosphatase was as high as 25 to 30 Bodansky units. The test is not conclusive but merely indicates that one should think in a certain direction.

The liver was doing a pretty good job on the whole, because it maintained the albumin at a level of almost 5 gm. per 100 cc. The globulin was slightly elevated, which implies an intrahepatic disturbance but does not prove it. There was dye retention of a moderate degree, which one would expect with this amount of jaundice. It does not help one to make a diagnosis. The cephalin-flocculation and the thymol-turbidity tests were not abnormal — at least not abnormal enough for any conclusions to be drawn from them. The fact that the cholecystogram did not reveal a well filled gall bladder is of little significance. If there is retention of bromsulfalein there is likely to be a retention of other more or less similar dyes that in itself can cause a complete nonfilling or partial filling of the gall bladder. At best this tells one that he does not know what is going on in the gall bladder, so I should disregard the cholecystogram in this case. There was no evidence of upper-gastrointestinal-tract cancer.

That leaves me with the physical examination and a history that clearly proved that there was disease in the liver. Whether there was disease elsewhere in the body remains to be proved. The disease in the liver on the basis of symptoms — namely, itching and jaundice — is associated with a faulty drainage of bile to the small bowel. The laboratory findings that favor such a conclusion are a slight elevation of alkaline phosphatase, definite reduction in excretion of the bromsulfalein and no demonstrable interference with the tests of liver function — the flocculation tests; the prothrombin time was not given here, but I assume that it was normal. Otherwise, it would have been mentioned.

Dr. Benjamin Castleman: That test was requested, but not done.

Dr. Jones: The fact that the urinary urobilinogen was high — 5 Ehrlich units — indicates that the obstruction was nowhere near complete. It is the sort of finding that can occur with intrahepatic disease as opposed to a partial block in the common duct at or near the ampulla or in some of the hepatic radicles. I think, then, that I am dealing with primary intrahepatic disease with partial block to the flow of bile through the bile canaliculi or the smaller biliary radicles, with some infection as evidenced by fever and modest leukocytosis — in other words, cholangitis or possibly cholangiolitis, if that differentiation really can be made with accuracy. This clinical story is a perfectly good one for the type of chronic liver disease that we call cholangiolitic biliary cirrhosis. With cholangiolitis of four years' duration one might expect to see xanthomatous deposits in the skin and an elevated cholesterol. The obstruction was intermittent, so that may be too much to expect in this case.

Are there any possibilities other than cholangitis with biliary cirrhosis? Although I should prefer cholangiolitic biliary cirrhosis as the most logical explanation, the patient could have had stone in the common duct with biliary cirrhosis on that basis. We have had a fair number of just such cases with no story of biliary colic, no impairment of gallbladder function and no evidence of stones. If stone was suspected, duodenal drainage might have produced diagnostic material, but it was not done. The chances of finding microscopic crystalline material, which is diagnostic, is very high — about 80 per cent; therefore, the procedure is worth the effort in doubtful cases.

Another possibility is some disease like lymphoma that might infiltrate the liver and spleen; I should expect that in four years' time there would be some enlarged lymph nodes. Itching is common in Hodgkin's disease, as is involvement of the liver. That is about as far as I should like to go.

I think the patient had cholangiolitic biliary cirrhosis. I think there are two therapeutic measures that one should consider; one is a punch biopsy of the liver to find out what it looks like; because of the intermittent nature of events the fever, jaundice and so on, it is much more logical to explore surgically. The first thing would be examination of the liver, and the second would be examination of the common duct. It would probably be in order to explore the common duct anyway.

A Physician: Would you consider a chronic infectious hepatitis with this picture?

Dr. Jones: Yes; but it would be very unusual indeed. As a rule with a postatrophic cirrhosis, which is I think what you mean, — namely, an initial infectious hepatitis going on progressively to a cirrhotic picture, — one would expect to find a relatively small liver; furthermore I should expect that there would be a great deal more interference with parenchymal-cell function. This looks as if the parenchymal function of the liver was good; the excretory function of the liver was interfered with.

A Physician: Would you have expected a large liver and spleen one year after the onset of fever symptoms without either jaundice or other signs of cholangitis?

Dr. Jones: I have seen patients who have been itching for two years without jaundice before the clinical picture developed at all. Whether they had liver and spleen enlargement at the time nobody knew because nobody examined them.

A Physician: Would you discuss the selection of anesthesia?

Dr. Jones: Nitrous oxide, oxygen and ether — I am assuming it was in the hands of a competent

anesthetist. Our studies have shown that there is no greater disturbance of liver function with nitrous oxide, oxygen and ether than there is with cyclopropane or a prolonged spinal or any other well given anesthesia. There is an impact on the liver that lasts for about ten to fourteen days, and then usually everything returns to its previous state.

DR. CASTLEMAN: Would you have done an aspiration liver biopsy before a laparotomy?

DR. JONES: I would have because it is so easy, provided the prothrombin time was normal. If one could assure himself without any undue hazard that there was biliary cirrhosis, I think one would be all the more enthusiastic about trying to find a gallstone.

DR. CASTLEMAN: I saw this patient clinically and agreed with Dr. Jones that the most likely diagnosis was biliary cirrhosis, either the intrahepatic type that he described or that due to chronic recurrent stones. I thought an aspiration liver biopsy should not be done because in any event operation would be necessary to find out if there were stones. In a needle biopsy one would not really be able to tell whether there were stones or whether there was just an intrahepatic cholangiolitic biliary cirrhosis.

DR. JONES: That is the correct way of putting it. Because this is a paper case to me, I am wondering about some other infiltrative disease that one could spot and thus avoid a laparotomy. I think there is enough justification for saying that there was intrahepatic block.

DR. PERRY J. CULVER: We were extremely impressed with how healthy the patient looked after four years of what had been diagnosed before entry here as chronic recurrent hepatitis.

DR. JONES: What do you mean by chronic recurrent hepatitis?

DR. CULVER: Viral hepatitis.

DR. JONES: I should not be able to make that diagnosis.

CLINICAL DIAGNOSIS

Intrahepatic biliary cirrhosis.

DR. CHESTER M. JONES' DIAGNOSIS

Cholangiolitic biliary cirrhosis.
?Stone in common duct.

ANATOMICAL DIAGNOSIS

Chronic recurrent hepatitis, viral type.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The patient had had a liver biopsy over a year before admission in another hospital, and the diagnosis of hepatitis was made. After seeing her, I, as well as the men who were taking care of her, had some doubts about that diagnosis; we thought it best to review the slides of the biopsy before anything further was done. The slides did show necrosis of liver cells with occasional mitoses and a definite portal cellular reaction invading the liver lobules — all in keeping with the viral hepatitis. With the definite evidence of hepatitis at least a year and a half before admission, Dr. Culver and I believed that aspiration biopsy rather than a laparotomy was clearly indicated. The biopsy also showed necrosis of the liver cells and mitotic figures and only a small amount of connective-tissue response. Dr. Jones said that it is the very rare case of hepatitis that will go on to a cirrhosis. This patient had not gone on to cirrhosis; at least this biopsy contained little fibrosis, most of it merely showing a chronic, persistent, active hepatitis.

DR. JONES: I think there is one more point to be made. A very small group of patients has been studied by Popper* in Chicago. These patients seemed to have had viral hepatitis and in addition had the unusual finding of pericholangiolitis, with neutrophilic infiltration around the cholangioles. That is rare indeed. There is a question whether this is the same disease that is ordinarily called viral hepatitis. The patient in the case under discussion had a clinical picture of fever and the clinical manifestation of cholangitis. Were there areas of neutrophil infiltration?

DR. CASTLEMAN: No; there were lymphocytes and monocytes but no neutrophils.

DR. JONES: That is the characteristic infiltrate in viral hepatitis.

*Popper, H. P. Personal communication.

CASE 39082

PRESENTATION OF CASE

First admission. A fifty-five-year-old merchant was admitted to the hospital because of sweating and fever.

On the day before admission he was somewhat constipated, and while attempting to have a bowel movement he became chilly, and shortly began sweating. He was drowsy, went to bed early, and four times during the night vomited pink material. The next morning he was still drowsy, had blurred vision and had a temperature of 101.8°F., so he was advised to enter the hospital.

Five years previously, on routine examination, he was found to have mild hypertension and diabetes mellitus. The diabetes was easily controlled by diet alone, and he felt well until two years before admission, when he had a sudden onset of left-sided weakness. He was treated for six weeks in another hospital and subsequently at a rehabilitation center, with gradual but incomplete recovery of function in the left arm and leg. Seven months before entry he had a one-week episode of fever, diagnosed as "virus infection"; the urine was said to be "infected" at that time. Review of systems and past history were otherwise noncontributory.

Physical examination showed an obese, hirsute, well developed, drowsy man, who appeared acutely ill. There were scattered rales and bronchial breathing over the chest bilaterally. The heart was slightly enlarged, the border of dullness extending to the left, and there was a Grade 2 apical systolic murmur. There was questionable resistance to palpation over the right upper quadrant of the abdomen. The prostate was twice the normal size. There was left hemiparesis, with generally sluggish reflexes, and an extensor plantar reflex on the left.

The temperature was 104°F., the pulse 120, and the respirations 36. The blood pressure was 130 systolic, 90 diastolic.

The urine was cloudy, had a specific gravity of 1.018 and gave a ++ test for albumin, a green sugar reaction and a negative reaction for bile and acetone; the sediment contained 10 red cells, 16 white cells with frequent clumps, a rare coarsely granular cast and a few bacteria per high-power field. Examination of the blood disclosed a hemoglobin of 15.5 gm. per 100 cc. and a white-cell count of 27,000, with 99 per cent neutrophils. The nonprotein nitrogen was 33 mg., and the blood sugar 260 mg. per 100 cc., and the carbon dioxide 25.5 milliequiv. per liter. A lumbar puncture revealed normal dynamics and a normal appearance of the spinal fluid, which was negative on cytologic examination, had a total protein of 50 mg. and a sugar of 170 mg. per 100 cc. and gave a gold-sol curve of 0001110201. The bromsulfalein test demonstrated 58 per cent retention of the dye after forty-five minutes. A roentgenogram of the chest showed the heart to be considerably enlarged, chiefly in the region of the left ventricle. The superior mediastinum was broad, apparently owing to a tortuous aorta and fairly prominent vena cava. The lung fields were clear. An intravenous pyelogram was unsatisfactory, but there was less excretion on the left. An electrocardiogram revealed a normal rhythm at a rate of 75, a PR interval of 0.16 second, low T waves in Leads 1, 2, 3, V_5 and V_6 and upright T waves in Leads V_1,V_2, V_3 and V_4. Cultures of urine showed no growth. Heterophil-antibody agglutinations for typhoid, paratyphoid and brucella organism were negative, as was a smear for malaria.

The patient was given penicillin, streptomycin and terramycin but continued to have irregular temperature spikes up to 101°F. On the ninth day cystoscopy was performed, and a markedly enlarged prostate was found. The left ureter could not be catheterized. On the next day slight jaundice was noted. The blood culture was reported as showing *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) overgrowing *Staphylococcus albus*. The nonprotein nitrogen was 31 mg., the albumin 3.48 gm., and the globulin 2.31 gm. per 100 cc., with an albumin-globulin ratio of 1.5. The stool showed a faint trace of urobilinogen; the urinary urobilinogen was 0.7 Ehrlich units. The serum bilirubin was 0.5 mg. direct and 0.9 mg. total, and the alkaline phosphatase 9.2 units per 100 cc. A repeat urine for urobilinogen contained frank blood. Cephalin flocculation was + in forty-eight hours. A Graham test revealed a nonfunctioning gall bladder and a suggestion of calcification above the right kidney.

The patient continued to have chills and an irregular, spiking fever, with a maximum temperature of 106°F., and although the physical examination remained unchanged the white-cell count rose to 51,000, with 97 per cent neutrophils, many of which were band forms. On the eighteenth day a blood culture grew *Alcaligenes faecalis*. An x-ray film of the abdomen demonstrated a 1-cm. calcific density in the left pelvis, and an intravenous pyelogram showed the left kidney to be larger than the right, with poorly defined margins. Excretion was slowed in the left kidney, and the left pelvis, calyxes and proximal ureter were dilated. The calcification lay in the position of the distal ureter, and there was evidence of prostatic enlargement. The fever gradually subsided, and on the thirty-second day a left nephrectomy was performed. The pathological diagnoses were renal lithiasis, with hydronephrosis, and acute and chronic pyelonephritis.

Postoperatively, the patient's general condition remained the same. He was afebrile, and urine output was adequate, but with a residuum of about 200 cc. The urine had a specific gravity of 1.008 and gave a ++ test for albumin, with 30 red cells and 60 white cells per high-power field in the sediment. He was discharged on the fiftieth day with arrangements for catheterization as necessary and instructions to return in a month for prostatectomy.

Second admission (seventeen days later). After a week at home the temperature returned to 101 to 102°F., and the patient became anorexic and dehydrated. The urethral catheter was replaced and streptomycin and penicillin administered, but without effect, and he was readmitted to the hospital. Physical examination and laboratory data were essentially unchanged. He was given streptomycin, aureomycin and terramycin. The urine output ranged from 500 to 1000 cc. daily, and his condition remained stable except for occasional hiccups until the seventh day, when severe dyspnea, cyanosis and tachycardia (rate of 180) suddenly developed. There were rales at both lung bases and a to-and-fro apical cardiac murmur. A roentgenogram of the chest showed no change from previous films. An electrocardiogram revealed sinus tachycardia (rate of 150), with slurred S waves. The QRS complexes were widened slightly up to an interval of 0.1 second, and there was an occasional premature ventricular beat. The T waves were low in all leads; there were no abnormal Q waves. The R waves were upright across the chest. The patient was digitalized and dyspnea decreased. A repeat electrocardiogram the next day showed normal rhythm at a rate of

100. The slurred S waves had disappeared, and the QRS complex was normal.

Distressing hiccups returned, and the temperature spikes became higher, up to 105°F. The spleen was easily palpable, and there was a question of a large, nontender right-upper-quadrant mass. The white-cell count was 15,400, with 83 per cent neutrophils. The urine was cloudy and dark amber, with a specific gravity of 1.018, and gave a ++ test for albumin; the sediment contained 20 red cells, 100 white cells and a few bacteria per high-power field. The serum sodium was 124.5 milliequiv., the chloride 91 milliequiv., the potassium 2.9 milliequiv., and the carbon dioxide 29.8 milliequiv. per liter; the nonprotein nitrogen was 24 mg., and the serum bilirubin 1 mg. direct and 1.4 mg. total per 100 cc.

On the tenth hospital day a cholecystotomy was done. On the next day the patient became unresponsive, with rapid, noisy respiration, a stiff neck and a rapid, regular heart rate. Blood cultures taken on the seventh and eighth days all yielded *Escherichia coli*, which was insensitive to streptomycin, aureomycin, terramycin and chloramphenicol. On lumbar puncture the cerebrospinal fluid was under an initial pressure equivalent to 220 mm. and a final pressure equivalent to 165 mm. of water after removal of 15 cc., was lemon-tinted and grossly cloudy, and contained 4500 cells per cubic millimeter, all neutrophils. Coma deepened, and he died on the thirteenth hospital day.

Differential Diagnosis

Dr. Allen G. Brailey*: In this case the nature of death seems fairly obvious; it is more difficult to guess how and where the fatal disease arose.

May I see the x-ray films?

Dr. Stanley M. Wyman: In the x-ray films of the chest the heart shadow is enlarged. The patient, however, is lying on his back so that part of the apparent enlargement is due to magnification. I think the superior mediastinal fullness is probably vascular in origin. The original pyelogram showed a large amount of material obscuring the kidneys, and the examination is unsatisfactory. A density overlying the left sacrum is seen that in subsequent examinations, a little more than two weeks later, has progressed downward somewhat; this is quite consistent with a large stone in the left lower ureter. On the second pyelogram the left kidney shows function that cannot be seen with any degree of certainty on the original examination. There is slight calcification in the left kidney.

Dr. Brailey: What about calcification above the right kidney?

Dr. Wyman: That is seen on this film of the gall bladder. I am not sure of its nature; I think it is a "red herring." One film from a negative barium-enema examination is included.

*Assistant physician, Massachusetts General Hospital.

Dr. Brailey: Is the liver size normal as far as you can tell?

Dr. Wyman: The liver is not grossly enlarged.

Dr. Brailey: Do you think this could be a dissecting aneurysm in the mediastinum?

Dr. Wyman: I doubt it seriously.

Dr. Brailey: On the final admission a to-and-fro apical murmur was heard. Was that due to a ruptured valve, to aortic regurgitation, to pericarditis or to something else?

Dr. F. Dennette Adams: May I make some corrections in the protocol that may help you? You can discount the bronchial breathing and the cardiac murmur; they were not heard by most observers. During the first few days we thought (and justifiably, it seems to me) that we were dealing with a case of urinary infection based on prostatic enlargement. The patient was promptly established on constant drainage and did very well for a few days. But he then began to have recurrent bouts of fever between which he was better. It was then that further studies were initiated.

Dr. Brailey: Was he afebrile for a while after constant drainage was started?

Dr. Adams: Yes; the temperature came down and it looked as though the Foley catheter and antibiotics had straightened him out. When we were about ready to send him home, the episodes of fever with elevated white-cell count began.

Dr. Brailey: This patient died as a result of overwhelming infection. As for the infection itself, I am embarrassed with riches. Four different organisms were cultivated from the blood, of which three were gram-negative bacilli. The *Staph. albus* can be ignored as a contaminant, but I am obliged to accept the other three as significant although I suspect that it was the resistant strain of *Esch. coli* that gave him the *coup de grâce*. But how does it happen that three organisms were grown? It is a curious fact, and one not easily explained; infections are not commonly due to multiple organisms. Even if several organisms are introduced into a wound, we believe that one quickly tends to "outgrow" the others.

This man had had a source of infection in the kidney for a long time, probably for years. It is not helpful that the protocol makes no mention of tenderness of either kidney area. In fact there is no mention of localizing tenderness of any sort. However, much of the time he was so sick that probably he was not very co-operative, and, furthermore, in fatal pyelonephritis or necrotizing papillitis, there may not be any renal pain or tenderness. I wonder whether cultures were taken from the excised left kidney and, if so, what organisms grew out.

If we assume for a moment that the fatal infection arose from pyelonephritic kidneys, when did it first burst its renal confines and invade the blood stream? I am told that the patient had a cerebro-

vascular accident two years before the first admission that resulted in left hemiplegia. Such episodes are very often due to emboli, but it is hardly credible that he had emboli to the kidneys or that he nursed a subclinical bacterial endocarditis for two years. Seven weeks before entry he had fever for a week, and urinary-tract infection was noted at that time. Perhaps he first had bacteremia at that time. The onset of the acute illness is carefully timed for me, and the suggestion seems to be made that there was some causal relation between straining at stool and the onset of chilliness and sweating. The chilliness and sweating in this case surely marked a rapid extension of infection, but it is difficult to see what his toilet activities could have had to do with that unless, conceivably, a small abscess in some organ ruptured and spilled pus directly into a vein. Such accidents must be rare but they have been described by Webber and Coe,[1] and such a hypothetical event would have the merit of explaining much of what happened to this man. It would explain the acute onset, and it would offer a reason for the culture of three separate organisms from the blood. However, the onset of acute pyelonephritis or papillitis is often as acute as this without obvious explanation.

It is hard to be sure of the kidney lesion. There are many factors in favor of necrotizing papillitis of the so-called subacute or protracted sort. The patient was a man. He had diabetes. It is interesting that the severity or mildness of the diabetes seems to bear no relation to the incidence of papillitis. The clinical course in papillitis is usually brief and stormy, and it is often complicated by overwhelming blood-stream infection. Against papillitis is the fact that kidney function remained satisfactory and azotemia did not develop. The majority of persons with necrotizing papillitis die of uremia but in 1950, Robbins et al.[2] reported 19 cases, in 5 of which the patients never showed nitrogen retention but died of septicemia, toxic hepatitis and other causes. Perhaps it is of only academic interest whether the kidney lesion is classified as papillitis or pyelonephritis. Either can lead to this sequence of events, and, after all, papillitis is probably only an especially severe and unique form of pyelonephritis. I expect that the liver showed a toxic hepatitis and perhaps multiple abscesses as well.

Did the patient have a bacterial endocarditis? If new heart murmurs of significance developed, perhaps endocarditis should be considered. There was no evidence of myocardial infarction. Presumably, the tachycardia was a toxic effect, and, in view of some changes in the T waves as reported, the rhythm probably arose from an ectopic focus near the node. A terminal meningitis obviously developed.

If I have drawn a true picture of the development of this man's fatal illness, why did he have an interval of freedom from fever during which it was hoped that he was convalescent? The left kidney, which was perhaps the chief original focus of the infection, had been removed, and he had had vigorous treatment with antibiotics, which may have suppressed the disease for the several days during which he appeared to be better. It is somewhat astonishing to read that the surgeons found the courage to remove the gall bladder on the second entry, but I suppose it was hoped that he had an empyema of the gall bladder whose removal would cure him.

Dr. Benjamin Castleman: A cholecystotomy was done; the gall bladder was not removed.

Dr. Brailey: Then the physicians caring for the patient thought that the patient had an empyema of the gall bladder and that drainage would cure it.

Finally, in retrospect, could anything more effective have been done to have averted the fatal outcome? Certainly, it is a great pity that the urinary-tract infection was not discovered at its onset and treated effectively from the start. Diabetes is a great handicap in the treatment of infection, and one wishes that the diabetes had been handled more effectively. If any effort was made to reduce his weight to normal it was unsuccessful. The organisms to which he succumbed belong to a class that in general do not respond well to antibiotics. Perhaps the strains that he harbored were hopelessly resistant to antibiotics from the beginning, but it is possible that a heavier dosage at the start would have helped him to get the upper hand before fatal resistance to drugs had developed.

I think that the diagnoses were chronic and acute pyelonephritis, with possibly necrotizing papillitis, bacteremia due to *Esch. coli*, multiple abscesses, meningitis and diabetes mellitus.

Dr. Adams: May I add that during part of the early hospital course the patient was so sick that it was impossible to pursue further investigations? An attempt was made to get retrograde renal studies, but the prostate was so large that the urologist was unable to pass a catheter into either ureter. Efforts to obtain intravenous pyelograms were hampered for several days by inability to clear out the bowel. When this was finally accomplished, we discovered what we had thought all along: that he had renal infection. We were next faced with the decision whether to go after the stone or do the simpler procedure, which was to drain the kidney through the back.

Dr. Brailey: I am not criticizing what was done in the hospital, but, after all, the situation had existed for months or years before any treatment was received.

Dr. Adams: I merely want to clarify the sequence of events after the patient came to the hospital. After removal of the kidney he did beautifully. During convalescence there was much deliberation whether to operate on the prostate. But he was so well and had been through such a serious illness

that we decided to give him a vacation and bring him back later for prostatectomy. He left the hospital in fine shape but got into more trouble during the period at home. The reason for the gall-bladder operation was that the bilary tract had been considered as the possible cause of the sickness during the first admission. During that time jaundice developed. It was postulated that he might have an infected gall bladder, perhaps with a stone in the common duct, and that our diagnosis of renal infection, which had not been proved at the time, was incorrect. On the second admission we were forced to reopen the question of the biliary tract.

DR. CASTLEMAN: Did you not feel a mass in the right upper quadrant?

DR. ADAMS: There was a good deal of discussion about that. Some of us believed that the abdomen was tender, with a poorly definable mass in the right upper quadrant. The second operation was done because we had to grasp at every straw. We continued to worry about infection in the kidney bed, although at no time, even when he had the "red-hot" kidney, did we find tenderness or any localizing sign.

DR. LORANDE WOODRUFF: This case was confusing because at no time was there any pain or tenderness over the left kidney. This lack of signs or local symptoms was one thing that stayed my hand for a long while. I could not be sure that the area of calcification seen in the plain film was a stone, and even if it was it might have been present for several years and had nothing to do with the acute illness. We needed additional evidence, which was finally supplied by the second pyelogram.

CLINICAL DIAGNOSES

Septicemia and meningitis due to *Esch. coli.*
Pyelonephritis.
Diabetes mellitus.

DR. ALLEN G. BRAILEY'S DIAGNOSES

Acute pyelonephritis, with ?necrotizing papillitis.
Bacteremia due to *Esch. coli.*
Multiple abscesses.
Meningitis due to *Esch. coli.*
Diabetes mellitus.

ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis due to gram-negative bacillus.
Septic infarct of right kidney.
Meningitis, subacute bacterial.
Ureterolithiasis, left.
(Cholelithiasis.)
Operations: nephrectomy, left, and cholecystotomy.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the operation during the final admission Dr. Leland S. McKittrick found a thin-walled gall bladder, normal except for some stones, which he removed; the bile appeared normal, and there was no inflammation of the wall. There was no evidence of residual infection in the kidney bed, and this was confirmed at the time of autopsy. The right kidney was swollen and contained one abscess that measured 3 by 2 cm. and was full of bacteria.

Microscopical examination showed that near the abscess was a large vessel containing a septic embolus. This came from large, fairly firm, granular vegetations attached to the aortic cusps that on microscopical examination were well organized and contained innumerable organisms. The rest of the kidney was not too diseased. We did find a stone in the lower left ureter that followed or was associated with the pyelonephritis or pyonephrosis on the left side.

I believe the sequence of events was an original renal infection on the left side due to the stones. As we know, a septicemia and also a bacterial endocarditis developed, and may well have been present after the first operation. Then perhaps he recovered, or the endocarditis was masked by the antibiotic treatment that he received for the renal infection. A flare up of the endocarditis with an embolus to the kidney followed. There was, as was suggested, a meningitis — almost certainly a bacterial, embolic type of meningitis — without any real infection in the brain. The spleen weighed 700 gm. and was septic.

DR. ADAMS: I did not misinform Dr. Brailey concerning that cardiac murmur. Looking through the record, I cannot find that it was heard. Furthermore, I doubt if anyone could have heard it in this very thick-chested man, who had constant noisy, grunting respirations. Dr. Gordon S. Myers, who examined his heart a few days before death, heard no murmurs at all.

DR. CASTLEMAN: Dr. Kunz, will you tell us about the cultures?

DR. LAWRENCE J. KUNZ: The organism isolated from the blood cultures on the last admission that were reported as *Esch. coli* were culturally consistent with the mucoid type of coliform bacteria. Just before the patient died, Dr. Thomas Paine took a subculture of one of those plates to do a tube-sensitivity test, since the organisms had been found resistant to all antibiotics, and discovered that it was an atypical *B. pyocyaneus* (*Ps. aeruginosa*), a very mucoid organism that is rarely seen but on prolonged cultivation did show pigment. I think that might resolve the difficulty of the three organisms in a single condition. The infection was quite resistant to all antibiotics tested.

REFERENCES

1. Webber, R. J., and Coe, J. I. Rupture of pyogenic hepatic abscess into hepatic vein: report of case. *Surgery* **27**:907-910, 1950.
2. Robbins, S. L., Mallory, G. K., and Kinney, T. D. Necrotizing renal papillitis: form of acute pyelonephritis. *New Eng. J. Med.* **235**: 885-893, 1946.

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THE COUNCIL MEETS AGAIN

The midwinter meeting of the Council of the Massachusetts Medical Society was held on February 4, with 245 councilors present. A number of committee reports were received and accepted with a minimum amount of discussion; certain others required considerable debate before their complete or partial disposal was effected.

On recommendation of the Subcommittee on Blue Cross–Blue Shield Problems, the Council unanimously approved the group enrollment in Blue Shield of members of the Massachusetts Medical Society. The report of the Committee on Public Health's Subcommittee to Consider the Union Health Department Law was accepted, with the proviso, mentioned in the report and emphasized by the Executive Committee, that the present Chapter 662 needs amendments that will modify or do away with the compulsory clause.

During consideration of that part of the report of the Committee on Finance relative to the needs and the activities of the Postgraduate Medical Institute, the announcement was made by the President of a grant of $7500 to the Institute by the Rockefeller Foundation.

The vigor of the debate over the recommendations of the Committee on By-Laws and Council Rules was exceeded only by the admirable imperturbability of its respected chairman. The recommendation that the present Advisory Board, consisting of the five most recent past presidents of the Society, "be given power to supervise the policies and property" of the Society and become, in effect, a governing board of trustees, was laid on the table. A majority of the councilors believed, apparently, that so much undefined authority should not be granted without still further consideration to a body so restricted in its composition.

After considerable debate the recommendation that the *By-laws* be so changed that "the President, in making his nominations, shall have previously requested from each district society the names of candidates for delegates to the American Medical Association and their alternates" was not accepted. It was replaced by the more drastic but more democratic resolution of the Worcester District Society that the duty of nominating the delegates be transferred from the President to the Committee on Nominations.

The report of the Committee on Hospital and Professional Relations also elicited a spate of discussion before its final acceptance. This committee has done yeoman service in narrowing the gap between the ratiocinations of the Medical Society and those of the Hospital Association to the degree where sparks of mutual understanding can now not infrequently bridge their nearest points.

WILLIAM MacCORMAC AND HIS AUTUMN HOLIDAY IN AMERICA

Sir William MacCormac, who visited the United States in 1883 and recorded his impressions in a diary, recently acquired by the Boston Medical Library, was an outstanding figure in British sur-

gery in the last three decades of the nineteenth century. D'Arcy Power, the surgeon-historian of a later period and no mean judge of his fellow men, characterized this six-foot-two Irishman as a surgeon of great industry, a master of detail and a rapid worker, whose bonhomie helped him to become a first-rate organizer. "At home in medical circles of Europe," wrote Power, "he broke down the insularity which still militates against the progress of English surgery, and he learned and taught what was done at home and abroad."

Written soon after MacCormac's death in 1901, these strictures could hardly be applied to British surgery in 1953, but MacCormac may be considered as a leader in developing an era of international exchange of medical thought and the growth of a mutual understanding now so freely expressed in medical and surgical congresses, exchanges of scholars, co-operative medical journals and a freedom of travel by modes of transportation little dreamed of in the gaslight era of MacCormac's time. He lived in the days when Sherlock Holmes and Dr. Watson were residing in Baker Street, not far from where MacCormac had his consulting room and home from 1871 to 1901 at 13 Harley Street.

When in the United States in 1883, moreover, Sir William and Lady MacCormac encountered electric lights for the first time. They were sailing from New York to Newport on the *Pilgrim* of the Fall River Line, which they described as "a floating palace." Passing down the East River they steamed under Brooklyn Bridge, the wonder of its time, saw a glorious sunset and, after a good dinner, retired to their cabin, there to find an electric light, which was described as follows by MacCormac:

> [It] turned on or off like gas, by a little tap placed at the same place as in a gas lamp. One had no trouble to light it, turn the tap, the arc was instantly incandescent and the room ablaze with light, and in a moment it could be put out again. The arrangement seemed very perfect, and was so novel to us that we tried the effect many times.

The simplicity of it all must have had a great and particular appeal to this brilliant surgeon, then, at the age of forty-seven, at the height of his career, who had first been a student of engineering at Belfast, before he turned to natural philosophy and finally medicine.

Born in 1836, the elder son of a distinguished physician of Northern Ireland who was a vigorous and pioneer advocate of the fresh-air treatment of pulmonary tuberculosis, young MacCormac, after obtaining his M.D. degree in 1857 in Belfast, studied with Langenbeck, Billroth and Esmarch in Berlin. This was the influential era of German surgery, and William's father saw that his gifted son received the best education offered by the leaders of Continental Europe. He returned to practice in Belfast, but the War of 1870 between France and Germany stirred the young Irishman and he, in spite of his German training and lasting friendship with his former teachers, enlisted on the French side, joined the Anglo-American Association for the care of the wounded and carried out a difficult assignment at Sedan after the battle on September 1, 1870, when he and some companions set up a hastily contrived hospital of 384 beds, where he did his best to follow out the new Listerian methods, then just coming into use.

When the War ended MacCormac settled in London, served as a surgeon at St. Thomas's Hospital, just moved to its new and impressive buildings on the south side of the Thames opposite Parliament, and became president of the Royal College of Surgeons. He will be best remembered for his contribution as general secretary of the International Congress of Medicine held in London in 1881. This brilliant meeting was his answer to the establishment of international good will in the field of medicine, and for this achievement his name will long be remembered. He turned on a new light, rapidly and efficiently, in world medicine, and it must have both fascinated and satisfied him to see the response to his endeavors as did the incandescent glow he witnessed for the first time on the Fall River boat two years later.

SECTIONAL MEETING OF AMERICAN COLLEGE OF SURGEONS

An event of interest to surgeons generally and to local readers of the *Journal* particularly is the Sectional Meeting of the American College of Surgeons in Boston, March 2-5, with headquarters at the Hotel Statler. This session, lasting four days instead of the usual two days devoted to sectional

meetings, will include panel discussions, symposiums, surgical clinics in 19 leading Boston hospitals, scientific papers and "ciné clinic" films. A committee on arrangements, consisting of Drs. Samuel F. Marshall, C. Stuart Welch, David D. Berlin, J. Englebert Dunphy, John W. Strieder and Howard Ulfelder, has set up a program covering general surgery, obstetrics and gynecology, ophthalmology, orthopedic surgery, otolaryngology, thoracic surgery and urology in which leading surgeons in each field will participate.

Boston accepts with pride the distinction conferred not only by the extended duration of the first sectional meetings to be so marked but also by the presence and participation of some of the leading surgeons in the country (not a few of whom, it should be noted, are native sons). On behalf of the honored city and its own readers, the *Journal* extends a hearty welcome to the College and to the surgeons who will take part in the sessions.

STUDENT PRIZE ESSAY

THE *Journal's* old friend, Dr. Wise, returns to its pages to remind fourth-year students that the prize-essay contest closes on March 15 as previously announced. The subject is an authentic case to be reported with a discussion and review of the important literature. The first prize is a check for $100, and the second prize a two-year subscription to the *Journal*.

For further particulars see the *Journal* of October 16, page 622, or write to the editor.

Dr. Wise, on a scholarly mission,
Makes note of a student tradition —
That when March is half through
The prize essays are due
In the* Journal's *acclaimed competition.

Suicides are increasing in France. Those in fear of the attentions of the government, pop out of the way of the police without apology.

Boston M. & S. J., *February 23, 1853*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

This year the Committee on Finance has voted a refund of $4000 to the district societies from the surplus in the General Fund at the end of 1952.

Members are reminded that the percentage of this sum that is allocated to their own district is determined by the number of dues from that district paid by March 1, 1953. Members who have not paid their dues by this date are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR., *Treasurer*

DEATHS

CHAMBERLIN — Harold A. Chamberlin, M.D., of Newtonville, died on December 12, 1952. He was in his sixty-third year.

Dr. Chamberlin received his degree from Tufts College Medical School in 1913. He was chief of service, Urology Department, Mount Auburn Hospital, surgeon-in-chief, Genitourinary Department, Boston Dispensary, consulting urologist, New England Hospital for Women and Children, urologist, Boston Floating Hospital, and professor of urology, Tufts College Medical School. He was a member of the American Urological Association and a fellow of the American College of Surgeons and the American Medical Association.

He is survived by his widow, a son and a daughter.

COLTON — Herbert P. Colton, M.D., of Middleton, died on January 25. He was in his sixty-fifth year.

Dr. Colton received his degree from Tufts College Medical School in 1918. He was superintendent of the Essex County Tuberculosis Hospital, having served for twenty-five years with the United States Public Health Service, and was a member of the American Trudeau Society.

He is survived by his widow, two brothers and a sister.

DOONAN — Henry E. Doonan, M.D., of South Hadley Falls, died on January 7. He was in his seventy-first year.

Dr. Doonan received his degree from Baltimore Medical College in 1908. He was medical examiner for Hampshire County and chairman of the South Hadley Board of Health and was a fellow of the American College of Surgeons and the American Medical Association.

He is survived by three sisters.

EIDAM — Carl H. Eidam, M.D., of Methuen, died on December 16, 1952. He was in his seventy-seventh year.

Dr. Eidam received his degree from College of Physicians and Surgeons, Boston, in 1897. He was the founder and first president of the Greater Lawrence Medical Society, and was a fellow of the American Medical Association.

He is survived by his widow, a son, a daughter, a brother, a sister and three grandchildren.

BOSTON MEDICAL LIBRARY

FOUR EARLY MEDICAL BOOKS PUBLISHED IN ENGLAND (1525–1527)

Four important publications of medicobotanical interest were issued in London between 1525 and 1527, three by an energetic printer and translator, Peter Treveris.

The first is the "Surgery" of Jerome of Brunschwig, an Alsatian army surgeon, who wrote principally on gunshot wounds. His book was first issued in the Strassburg dialect of German and published in Strassburg by Johann Grüninger in July, 1497. Containing 48 large and 13 small woodcuts, *Das Buch der Cirugia* is one of the most prized of the medical incunabula. Quickly recognized for its worth, Brunschwig's "Surgery," with its striking illustration, received an unauthorized printing by Schönsperger, of Augsburg, within six months. To offset this rival edition, also well printed, Brunschwig promptly issued a new edition, with additions and corrections. The translation into English, printed by Peter Treveris, of Southwarke, in 1525, was entitled *The Noble Experyence of the Vertuous Handy Worke of Surgeri Practysyd & Compyled by the Moost Experte Master Jherome of Bruynswyke*. Treveris, who may have made the translation, considered the book "necessary & profytable for surgyans as wel for them that have conynge as for them that be lerners." Thus it served, the first surgical book in English, for both surgeons and students. In spite of the omission of much of the text and many of the illustrations from the original editions, the English translation preserved the essence of the work with the description of ligature of vessels and the instructions on reduction and immobilization of fractures.

Although Jerome of Brunswick has not been awarded a high place in medical history, a careful reading of this book leads one to believe that he was a scholarly observer who drew many valid conclusions from his practical surgery on the field of battle. The striking illustration on the title page of the man being trephined for a head wound shows marked powers of observation. The paralysis of the right side of the face is well shown; it is clearly of the peripheral type, with the wide palpebral fissure and smooth brow. A third-nerve palsy is illustrated on the other side, the eye being pulled to the outer corner by the unopposed action of the sixth nerve, with the dilated pupil, the result of unrestrained sympathetic stimulation. A paralysis of the left side of the tongue is also well shown. This drawing resulted from more than a hasty glance by the surgeon. The book, moreover, contains much good advice to students and young surgeons and was certainly worthy of the folio volume provided by Treveris. One only wishes that the whole of the book with all the illustrations had been included in the first important "Surgery" to appear in England.

The book also contained as well the anatomy of the body of a man and an "antidotharius" on the making of plaster, powders and dressings for wounds. Many instruments are illustrated in anticipation of Paré, who followed Jerome in the sixteenth century.

The publication of Brunschwig's book in 1525 was timely. Henry VIII, then thirty-four years of age and an ardent and skillful horseman, frequently "carried off the palm in jousts and tournaments through his own prowess." (MacNalty, A. S. *Henry VIII. A Difficult Patient.* 202 pp. London: Christopher Johnson, 1952. P. 89.) He sustained a severe head injury in 1524 in tilting when a spear struck his helmet and threw open the visor. Again, he was almost drowned by falling into a ditch while hawking in 1525. Other injuries and narrow escapes from death occurred in subsequent years, and his six medical advisers, including Sir William Butts and Thomas Linacre, found the post as physician to the King an onerous one.

The second book, *The Grete Herball*, was translated from the French by Peter Treveris, the printer of Brunschwig's *Surgeri*, and issued from his press in Southwarke in 1526. Its predecessor, *Le grant herbier*, was one of the many fifteenth-century French herbals, dealing with medicinal plants and the virtues of herbs as remedies used in the treatment of disease. This was one of the most popular of the early herbals, compiled from sources going back into the Middle Ages. The book printed by Treveris became the most famous of the early English herbals. It was preceded in England by only one other herbal, issued by Richard Banckes in 1525 and recently published in facsimile from the rare copy in the British Museum.

The book is similar in appearance to the Brunschwig "Surgery" and, indeed, contains the same woodcut of the skeleton as a frontispiece. Treveris was so proud of his previous book that he mentions the "Surgery" in the title of the "Herball," published the next year.

An important part of herbal medicine was the preparation of the herbs by distillation. To Hieronymus Brunschwig, the surgeon, one also turns for the most complete treatise of the time. This, *The Vertuose Boke of Distyllacyon*, was translated and published by Laurence Andrew in London in 1527. It describes the elaborate apparatus used in the technical procedure of preparing herbs. The printing and illustrations are not as fine as those in the books by Treveris.

The fourth book deals with a study of urine, one of the most valuable aids to diagnosis known to the sixteenth-century physician. Urinalysis was developed to such an extent that the physician often made the diagnosis without ever seeing the patient. The book was also to be used by the patient so that he could properly describe the urine to his physician. The folio, *The Judycyall of Uryns*, was also published by Peter Treveris about 1527.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The March schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Salem	March 2	Paul W. Hugenberger, M.D.
Gardner	March 3	Carter R. Rowe, M.D.
Haverhill	March 4	William T. Green. M.D.
Greenfield	March 5	Charles L. Sturdevant, M.D.
Brockton	March 5	George W. Van Gorder, M.D.
Lynn*	March 9	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Lowell	March 13	Albert H. Brewster, M.D.
Springfield	March 17	James D. Fisher, M.D.
Pittsfield	March 18	Edward J. Coughlin, Jr., M.D.
Fall River	March 23	David S. Grice, M.D.
Hyannis	March 26	Paul L. Norton, M.D.
Worcester	March 27	John W. O'Meara, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	March 3, 10, 17, 24, 31
Fitchburg	March 4, 11, 18, 25

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

NONCLINICAL NOTES

LASKER AWARD

Dr. Paul D. White, of Boston, clinical professor of medicine at Harvard Medical School and chief consultant to the National Heart Institute, has been named as first recipient of the Albert Lasker award for distinguished achievement in the field of cardiovascular disease.

NEW DENTAL DEAN

Dr. Raymond J. Nagle, of Boston, president of the New England Association of Dental Examiners, has been appointed dean of New York University College of Dentistry, it was recently announced.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held January 15, 1953, it was voted to restore the registration of Dr. Thomas P. Beatty, of South Boston, Massachusetts.

Robert C. Cochrane, M.D.
Secretary

State House
Boston

STRESS AND THE ADAPTIVE HORMONES

To the Editor: In perusing the current literature with which *Annual Reports on Stress* is concerned, we note that an ever-increasing number of its articles deal with problems pertaining to research on "stress" and the so-called "adaptive hormones" (ACTH, STH, corticoids, adrenergic substances and so forth).

We are writing to you because, in our opinion, the success of research in this complex and rapidly developing field largely depends upon the prompt availability and evaluation of relevant publications, a task for which we should like to solicit the assistance of your readers.

In 1950 the Institute of Experimental Medicine and Surgery of the University of Montreal initiated the publication of a series of reference volumes entitled "Annual Reports on Stress" (Acta Medical Publishers, Montreal) in which the entire current world literature is surveyed every year (usually between 2000 and 4000 publications). Up to now, we had to compile the pertinent literature partly from medical periodicals, monographs and abstract journals and partly from reprints sent to us by the authors themselves. Of all these, reprints proved to be the best source of data that we considered to deserve prompt attention in our annual reports. Hence, in the past, we have sent out several thousand individual reprint requests to authors whom we knew to be currently engaged in research on stress and allied topics. Even this procedure did not give us the wide coverage that would be desirable, because it is materially impossible to communicate with all these authors individually and it often takes too much time to get the requested reprints.

It is evident that to ensure prompt inclusion of publications in the annual reports, these surveys must develop into a co-operative effort between the authors of original papers and the reviewers. This co-operation was greatly enhanced of late by the publication of announcements, in several medical journals, encouraging investigators interested in stress research to send us their reprints for this purpose as soon as they become available.

We should be grateful if by the publication of this note, you would also bring this problem to the attention of your readers.

Hans Selye, M.D., Ph.D., D.Sc., F.R.S.(C),
Professor and Director,
Institute of Experimental Medicine and Surgery
University of Montreal

Alexander Horava, M.D.
Co-author, Annual Reports on Stress

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the Boston City Hospital House Officers' Association will be held in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital, on Tuesday, March 3, at 7 p.m. John Parks, M.D., professor of obstetrics and gynecology, George Washington University School of Medicine, will speak on the subject "Some Medical, Psychiatric and Surgical Considerations in Vulvar Lesions." Discussers will be Drs. Joe V. Meigs, Louis E. Phaneuf and Somers Sturgis.

All interested persons are invited to attend.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, March 10, at 8 p.m. The following program will be presented by the Department of Anatomy, Harvard Medical School, George B. Wislocki, presiding:

Histochemical Demonstration of the Sites of Sulfhydryl and Disulfide Groups in Tissue. Russell J. Barrnett.

Chemical Morphology of the Retina. Richard L. Sidman and George B. Wislocki.

Experimental Studies on the Blood Brain Barrier of the Rat. Elizabeth H. Leduc.

Studies on the Fine Structure of Ciliated Epithelium with the Electron Microscope. Don W. Fawcett.

Some Aspects of Hibernation in Mammals. Charles P. Lyman.

AMERICAN ACADEMY OF ALLERGY

The ninth annual meeting of the American Academy of Allergy will be held at the Hotel Statler, Boston, on February 26, 27 and 28, under the presidency of Dr. Walter S. Burrage, of Boston. A scientific program, consisting of 26 papers presented by members, is to be supplemented by presentations of guest speakers on topics of hypersensitivity and immunity as related to various aspects of internal medicine. Among the latter are "Immunological Aspects of Blood Dyscrasias," by William B. Castle, M.D., Professor of Medicine, Harvard Medical School, and "Some Problems Concerned with the Interpretation of Side Reactions of Antibiotics," by Chester S. Keefer, M.D., Wade Professor of Medicine, Boston University School of Medicine. Scientific and commercial exhibits will be on display during the two and one-half days of the meeting.

The American Academy of Allergy came into being in 1943 through the ratification of the merger of its two parent societies, the Society for the Study of Asthma and Allied Conditions and the American Association for the Study of Allergy, both founded in 1923. These societies, organized almost simultaneously, were the first in any country to be established for the purpose of advancing the knowledge and practice of allergy. Many allergists eventually became members of both these earlier organizations so that their rosters contained a nationwide distribution even prior to their amalgamation.

The coming meeting of the Academy represents the thirtieth anniversary of uninterrupted activities of these three societies. Members of the medical profession are cordially invited to attend this meeting.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 20. New England Center Hospital House Officers' Association. Page 124, issue of January 15.

FEBRUARY 20–28. Springfield Hospital Educational Program. Page 164, issue of January 22.

FEBRUARY 20–MARCH 27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.

FEBRUARY 23 AND 24. American College of Surgeons. Page 42, issue of January 1.

FEBRUARY 23–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

FEBRUARY 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

FEBRUARY 25–APRIL 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

FEBRUARY 26–28. American Academy of Allergy. Notice above.

MARCH 2. New England Cardiovascular Society. Page 308, issue of February 12.

MARCH 2–5. Sectional Meeting of American College of Surgeons. Hotel Statler, Boston. Page 350.

MARCH 2–5. New Orleans Graduate Medical Assembly. Page 828, issue of November 20.

MARCH 2–27. Consultation Clinics for Crippled Children in Massachusetts. Page 353.

MARCH 2–APRIL 20. Hartford Medical Society. Page 42, issue of January 1.

MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

MARCH 3. Boston City Hospital House Officers' Association. Page 353.

MARCH 4. Massachusetts School Physicians' Association. Page 266, issue of February 5.

MARCH 7. Antibiotics: Specific Indications. Drs. Maxwell Finland and Louis Weinstein. Mount Auburn Hospital, Cambridge. 10:05 a.m.

MARCH 8–10. Alumni Postgraduate Convention. College of Medical Evangelists. Page 266, issue of February 5.

MARCH 10. Harvard Medical Society. Page 353.

MARCH 11 AND APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

MARCH 17. South End Medical Club. Page 307, issue of February 12.

MARCH 25. Cutter Lecture. Page 307, issue of February 12.

MARCH 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

APRIL 10–12. American Association of the History of Medicine. Page 308, issue of February 12.

APRIL 15. Massachusetts Academy of General Practice. Spring Clinical Assembly. Hotel Shelton, Boston.

APRIL 16–18. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 307, issue of February 12.

APRIL 19–24. National Industrial Health Conference. Page 308, issue of February 12.

APRIL 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

FEBRUARY 23–MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

FEBRUARY 24.
MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 26

THURSDAY, FEBRUARY 26

*All-day meeting. American Academy of Allergy. Hotel Statler.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Basilar Artery Stenosis and Basilar Aneurysm. Dr. Derek Denny-Brown. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, FEBRUARY 27

*All-day meeting. American Academy of Allergy. Hotel Statler.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pulmonary Conference. Drs. Kane, Etsten, Woods and others. Stearns Auditorium, New England Center Hospital.
*4:00–6:00 p.m. X-ray Conference. Drs. Sosman and Ferguson. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, FEBRUARY 28

*American Academy of Allergy. Hotel Statler.
*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 2

Sectional Meeting, American College of Surgeons. Hotel Statler.
*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.
*8:00 p.m. New England Cardiovascular Society. John Hancock Hall, 180 Berkeley Street.

TUESDAY, MARCH 3

Sectional Meeting, American College of Surgeons, Hotel Statler.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Some Medical, Psychiatric and Surgical Considerations in Vulvar Lesions. Dr. John Parks. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, MARCH 4

Sectional Meeting, American College of Surgeons. Hotel Statler.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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1 Schoenheimer, R., Ratner, S., and Rittenberg, D., J. Biol. Chem., 127:333, 1939 and 130:703, 1939.

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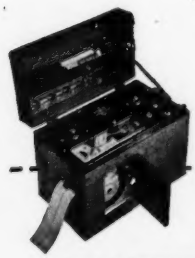

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